The Journal of Pediatrics

VOL. 42 MAY, 1953 No. 5

VACCINIA. PASSIVE IMMUNITY IN NEWBORN INFANTS

I. PLACENTAL TRANSMISSION OF ANTIBODIES

II. RESPONSE TO VACCINATIONS

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I. PLACENTAL TRANSMISSION OF ANTIBODIES

A HEMAGGLUTINATION-inhibition test for the determination of vaccinia antibodies in serum was first described by Nagler.[5] It has been used extensively by us in a standardized form.[2] Collier[3] has utilized a modification of the method in his study of adults. The present report deals with the determination of the titer of vaccinia antibodies in the sera of 182 mothers at term and in the cord blood of their newborn offspring. Of the mothers, 102 had been vaccinated within the past five years, while 80 had been vaccinated more than five years ago.

METHODS

A standardized procedure of determining vaccinia hemagglutination-inhibition antibodies in serum has been described previously.[2] A suspension of vaccinia-infected allantoic membranes is used as the antigen. Fowl cells susceptible to hemagglutination with the vaccinia-variola group of viruses are utilized in a concentration of 0.5 per cent in Alsever's solution. A single hemagglutinating unit is defined as that dilution of the antigen which produces definite hemagglutination of 0.25 c.c. of a 0.5 per cent suspension of vaccinia-sensitive fowl cells. The specificity of this reaction is shown as follows:

(1) Serum of vaccinated individuals inhibits this agglutination to a reproducible titer.

(2) There is failure of inhibition of agglutination by sera of nonimmune rabbits. Sera for antibody determination are diluted in 10 Kahn tubes in twofold dilution in 0.85 per cent saline solution (1:5 to 1:2560). The volume of diluted serum is 0.25 ml. To the serum dilutions, 0.25 ml. of antigen dilution containing two hemagglutinating units is added. Known positive and negative control sera are included. An antigen control is set up in which the antigen dilution used in the test is diluted in saline. Racks are shaken and incubated for one hour at

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The Editors of *The Yale Journal of Biology and Medicine* have granted permission to reprint portions of this article which previously appeared in the February, 1952, issue of that journal.

35° to 37° C. Then 0.25 ml. of 0.5 per cent fowl cell suspension is added, the racks shaken, and allowed to stand at room temperature until the cells are settled. After one hour, the pattern of sedimented cells is examined. The greatest serum dilution which produces complete inhibition of agglutination is recorded as the hemagglutination-inhibition titer of that serum. The tube containing this dilution should present the same pattern as a control tube with 0.25 ml. of vaccinia-

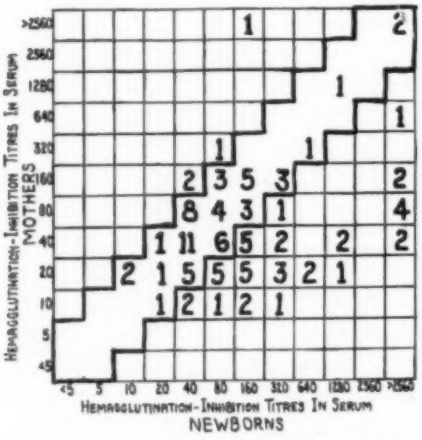

Chart 1.—Hemagglutination-inhibition titers in serum of 102 mothers (vaccinated within five years) and their newborn infants. Figures represent the number of instances in which the mother's titer and that of her newborn infant were found at the levels indicated. All numbers within the blocked area represent instances in which the mother's titer was found to be identical to that of her infant. Numbers to the right of the blocked area indicate instances in which the infants' titers were significantly higher than their mothers'.

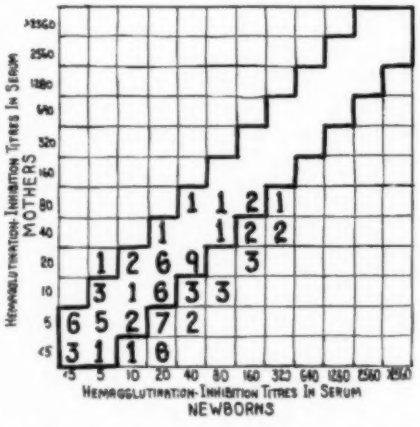

Chart 2.—Hemagglutination-inhibition titers in serum of 80 mothers (vaccinated over five years ago) and their newborn infants. Figures represent the number of instances in which the mother's titer and that of her newborn infant were found at the levels indicated. All numbers within the blocked area represent instances in which the mother's titer was found to be identical to that of her infant. Numbers to the right of the blocked area indicate instances in which the infants' titers were significantly higher than their mothers'.

sensitive red cell suspension and 0.5 ml. of saline. The negative control serum should show no inhibition of agglutination, while the positive control should show inhibition within one dilution of its usual titer.

RESULTS

Serologic studies were performed on 182 mothers at term and on cord bloods of their 182 newborn infants. Charts 1 and 2 give the number of instances in which the mother's antibody titer is present at the indicated level, then plotted against the antibody titer of the serum of her own newborn infant. Chart 1 refers to the mothers vaccinated within five years and their newborn infants. Chart 2 refers to the mothers vaccinated more than five years ago and their newborn infants. Where the titers of the mothers' serum and of their newborn infants are either identical or differ by one serum dilution in either direction—the latter differences being considered to be within the error of the tests—they are listed in the area enclosed by the heavy lines. Fig. 1 summarizes these data. They show that of 102 mothers vaccinated within five years, only 4 per cent have antibody levels significantly higher

than their own newborn infants, while 40 per cent have significantly lower antibody levels than their own newborn infants. Of 80 mothers vaccinated over five years ago, only 1 per cent shows antibody titers significantly higher than their own newborn infants, while 37 per cent have significantly lower antibody titers.

In order to test whether these higher titers, in fact, represent specific antivaccinia substance, complement fixation tests also were performed on the sera of 141 of the infants and their

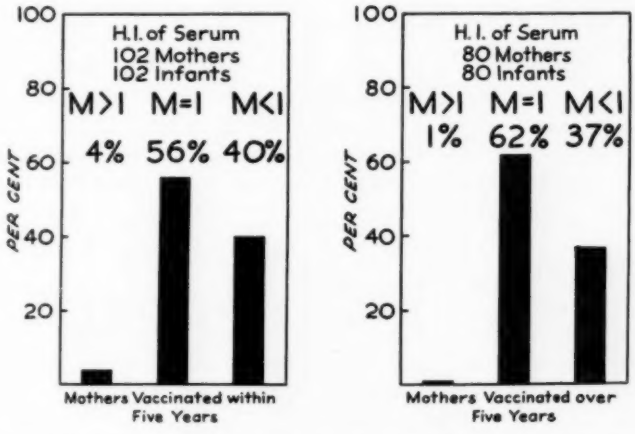

Fig. 1.—Hemagglutination-inhibition antibody titers in the serum of 182 mothers and their newborn infants. Of 102 mothers vaccinated within five years, 40 per cent have significantly lower antibody titers than their own newborn infants. Of 80 mothers vaccinated over five years, 37 per cent have significantly lower antibody titers than their own newborn infants.

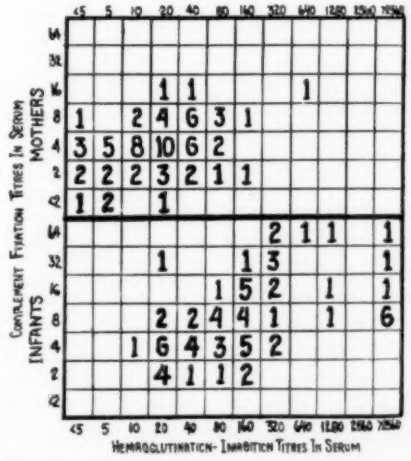

Chart 3.—Complement fixation titers in the serum of mothers and their infants in 141 instances in which the infants had shown higher hemagglutination-inhibition titers than their mothers. The complement fixation titers of these infants are also significantly higher than those of their mothers.

mothers. Chart 3 shows that, in general, newborn infants who have hemagglutination-inhibition titers higher than their mothers also show higher complement fixation titers. Fairly good correlation between these two very distinct antibodies is apparent, indicating presence of a specific immune substance.

DISCUSSION

The findings of consistently higher antibody titers in the blood of newborn infants, when compared to their own mothers, are of great interest and are not readily explained. They suggest that actual immunity substance is being measured and this tends to be borne out by the preliminary clinical experiments subsequently described. The higher concentration may be explained on the basis of concentration in the placenta and corresponding diaplacental transfer. This has been discussed by Doerr.[4] Such passively transferred and, perhaps, enhanced immunity immediately following smallpox vaccination of the mother may have definite clinical significance in pediatrics.

SUMMARY

1. A comparison of the hemagglutination-inhibition titers of 182 mothers at term and their newborn infants reveals consistently higher titers in the infants in a significant number of cases.

2. Mothers vaccinated within the past five years have higher titers than those vaccinated earlier.

3. Infants of mothers vaccinated within the past five years have significantly higher titers than those whose mothers were vaccinated more than five years ago.

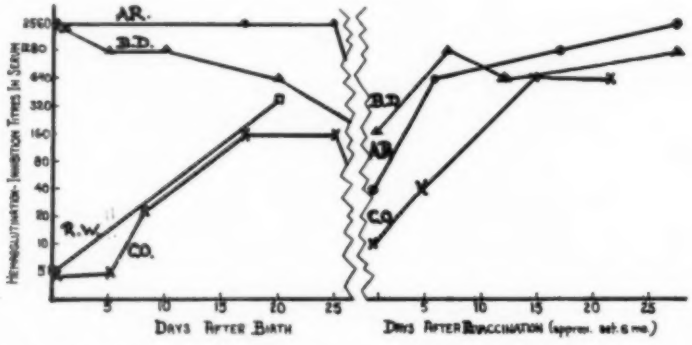

Fig. 2.—Hemagglutination-inhibition titers of four newborn infants at time of birth and following vaccination at 5 days of age. Three of these infants were revaccinated at around 6 months of age and their antibody response shown.

II. Response to Vaccination

A preliminary attempt to evaluate the significance of occasional high levels of hemagglutination-inhibition antibody titers in cord blood was made. Four newborn infants were vaccinated on the fifth day of life. Two of these had had very high titers in the serum, while the other two had had very low titers. The two infants (A. R. and B. D.) with high antibody titers failed to show any skin reactions at the site of vaccination, despite three attempts

at vaccination. The two (R. W. and C. O.) with low antibody titers had a "vaccinia-take," with maximum skin reaction occurring on the tenth day after the vaccination. Fig. 2 shows the serologic response of these four infants.

At approximately 6 months of age, repeat vaccinations were performed on three of the four infants. Prior to revaccination infant A. R. had a residual antibody titer of 1:40, while B. D. had a titer of 1:160, and infant C. O. had a titer of 1:10. Revaccination of these three infants produced no allergic or immune early response in patients A. R. and B. D., and resulted in an early sensitivity response in infant C. O. followed by a typical vaccinoid reaction, maximal on the sixth day.

Infants A. R. and B. D. developed a reaction maximal on the fifth and sixth days, respectively. Had it not been for the absence of an early sensitivity type of reaction, indicating a lack of previous antigenic experience to the virus, these reactions would undoubtedly be called vaccinoid. However, in the absence of this type of sensitivity reaction and the known findings of a high titer of passively acquired antibodies, it is suggested that these were modified primary "vaccinia takes." A third vaccination performed on these two children (A. R. and B. D.), at the age of one year, resulted in a sensitivity type or immune early reaction maximal on the second day after vaccination.

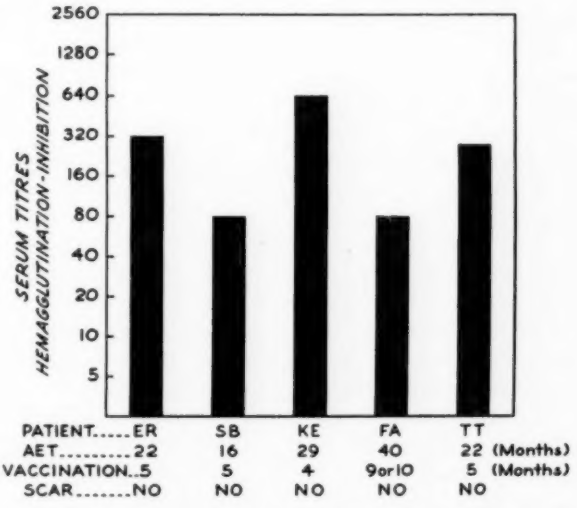

Fig. 3.—Hemagglutination-inhibition titers at the time of their final revaccination of five children who had received three or more unsuccessful vaccinations.

Antibody studies were performed on an additional five children, who had been described by their physicians as entirely resistant to repeated vaccinations (Fig. 3). The serum titers of these five children seen at 22, 16, 29, 40, and 22 months, respectively, are shown in Fig. 3. Patient E. R. had first been vaccinated at 5 months of age without result. At 22 months his

hemagglutination-inhibition titer was 320. He had, at that time, received four vaccinations at different sites but failed to show a scar. S. B. was first vaccinated at 5 months of age and failed to respond. At 16 months of age, her antibody titer was 80. She had been vaccinated on six occasions, with active material at different sites and failed to develop a reaction. K. E. was first vaccinated at 4 months of age and at 29 months showed a titer of 640. He had had three unsuccessful vaccinations. F. A. was first vaccinated at 9 or 10 months of age without success. At the age of 14 months, his titer was 80, after four unsuccessful vaccinations. T. T. was first vaccinated at 5 months of age, unsuccessfully. At 22 months of age his antibody titer was 320, after eight unsuccessful vaccinations. None of these children showed scars of primary vaccination. These children were then revaccinated with highly active vaccine and observed daily. Patient S. B. failed to respond in any way as had previously been indicated by referring physician. The other four children uniformly showed an immediate reaction which was maximal within seventy-two hours after revaccination.

DISCUSSION

Failure to react in any way to vaccination has in the past invariably been ascribed to faulty technique or the use of inactive inoculant. Over the years, however, pediatricians have pointed to instances where children did not respond to vaccination with material known to be highly active in other cases. The observations on two infants herein reported suggest that, at least early in life, passively acquired immunity might, in fact, interfere with dermal infection to live vaccinia virus and result in a true "no take." The immediate reaction, reaching its maximum within seventy-two hours after vaccination, is an allergic reaction to vaccinia antigens. It denotes previous antigenic experience, usually through successful vaccination.[1, 6, 7] This reaction is not seen in unvaccinated infants but is present virtually in all revaccinated children.

In the absence of an early sensitivity response suggestive of previous antigenic experience, accelerated vaccinia resembling a vaccinoid reaction may represent modification of the infection by passively acquired immunity present in the tissue.

The four children who had had many vaccinations early in life and who, following these repeated vaccinations and in the absence of scars indicating primary vaccinia, showed a sensitivity type of immediate reaction must be classified as having acquired active immunity under the cover of passive immunity transplacentally transmitted. The phenomenon of passive-active immunization is of interest in our present concept of immunology in other fields. Conceivably the utilization of active immunization under the cover of passively supplied antibodies might come to the fore in the field of poliomyelitis immunization. It has already found its place in veterinary medicine.

SUMMARY

1. Two newborn infants with high hemagglutination-inhibition antibody titers in their sera could not be successfully vaccinated in the first two weeks of life and these may represent instances of actual "no takes."

2. Two newborn infants with low hemagglutination-inhibition antibody titers in their sera were successfully vaccinated in the first week of life and demonstrated a rise in antibody titer.

3. At the age of 6 months repeat vaccination of the two infants with high titers resulted in a skin reaction maximal on the fifth and sixth days, respectively, in the absence of an earlier sensitivity type of reaction. This suggests that no previous antigenic experience had occurred and that the present response was, in fact, a modified vaccinia or accelerated primary response. Serologic data on these patients have been presented.

4. Five children who have had three or more unsuccessful vaccinations in infancy were again vaccinated. Their serum prior to this final revaccination showed considerable antibodies. Considering that the children were between 16 and 40 months of age, transplacental passive immunity would have been expected to have entirely waned. It is suggested that active immunization, through repeated vaccinations, was accomplished under the cover of transplacentally acquired passive immunity and that a true antigenic experience occurred at some stage in four out of the five children, as judged by the observed immediate reaction ordinarily acquired only through successful primary vaccination. This phenomenon is presumed to be an instance of passive-active immunization and has considerable implications in explaining heretofore puzzling reactions to smallpox vaccination of children.

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EFFECTIVENESS OF PENICILLIN ADMINISTERED ORALLY AT INTERVALS OF TWELVE HOURS

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IT IS firmly established that penicillin is absorbed from the gastrointestinal tract and that therapeutically effective serum levels can be obtained after the ingestion of adequate doses. Since 1945, there have been many reports of the clinical effectiveness of orally administered penicillin. In spite of the fact that the parenteral administration of potassium penicillin-G two or three times a day has been employed with excellent results, it is generally recommended that the oral preparations be administered at short intervals of time. A few authors,[1, 2] however, have recommended the oral administration of penicillin at intervals of eight or twelve hours. It was the purpose of this study to investigate the therapeutic effectiveness of penicillin administered orally at relatively long intervals of time in infants and children. The results obtained in treating common infections encountered in infants and children with penicillin administered orally at intervals of four hours have been compared with the results obtained when the drug was administered at intervals of twelve hours. The series includes 292 children who were observed through 308 infections.

METHOD OF CLINICAL INVESTIGATION

Subjects.—Infants and children from the outpatient and inpatient departments of St. Christopher's Hospital for Children who had a variety of infections were assigned to one of the three therapeutic programs. The infections encountered in this series of cases were considered sufficiently severe to require antibacterial therapy. No patient had received any antibacterial therapy for the current infection.

Therapeutic Programs.—Three therapeutic programs using orally administered penicillin were compared. In the first program, 200,000 units of potassium penicillin-G* in a liquid vehicle were administered as an initial dose, followed by 100,000 units of the same preparation at intervals of four hours. The second program consisted of the oral administration of 300,000 units of the same potassium penicillin-G preparation at intervals of twelve hours. The third program consisted of the oral administration of 300,000 units of procaine penicillin† at intervals of twelve hours. The administration of penicillin did not coincide with the ingestion of meals or the feeding of formulas.

Clinical Procedure.—When a patient was admitted to the therapeutic evaluation study, he was assigned to one of the three programs. Suitable material for cultures was obtained as indicated by the nature of the disease. This material was inoculated according to standard bacteriologic techniques and

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*The potassium penicillin-G preparation was supplied by Smith, Kline & French Laboratories, Inc., as a liquid preparation containing 50,000 or 100,000 units per teaspoonful (5 ml.).

†The procaine penicillin preparation was supplied by Smith, Kline & French Laboratories, Inc., as a liquid suspension containing 250,000 units per teaspoonful (5 ml.).

incubated under aerobic and anaerobic conditions. Penicillin sensitivity studies, using the technique of Bondi and associates,[3] were performed on each specimen.

The patient's response to therapy was noted during his period of hospitalization and at subsequent visits to the outpatient department. Material from appropriate areas was obtained during the course of therapy for the bacteriologic and penicillin susceptibility studies described above. A small sample of capillary blood was obtained at least once from most patients during the course of therapy for the determination of serum penicillin concentration by a microtechnique adapted from the method of Rammelkamp.[4]

The patients were observed until they had recovered from their infections. More than 70 per cent of the total number of patients were examined three or more times.

ANALYSIS OF CLINICAL RESULTS

Distribution of the Patients.—The number of patients in the various age groups assigned to each of the therapeutic programs is noted in Table I. The number of patients in each program is comparable. The distribution of patients by age in the various programs is quite similar except for the age group of 0 to 2 years in which fewer patients were treated with procaine penicillin than with potassium penicillin-G by either dosage schedule.

TABLE I. DISTRIBUTION OF PATIENTS ACCORDING TO AGE AND DOSAGE REGIMEN

AGE RANGE	DOSAGE REGIMEN		
	K-PEN-G, 4 HR.	K-PEN-G, 12 HR.	PROC. PEN.—12 HR.
0-2 yr.	35	36	27
2-4 yr.	26	37	37
4-6 yr.	7	9	15
Over 6 yr.	19	21	23
Total No. of patients	87	103	102
Total No. of infections	91	111	106

TABLE II. DISTRIBUTION OF INFECTIONS ACCORDING TO DOSAGE REGIMEN

DIAGNOSIS	DOSAGE REGIMEN		
	K-PEN-G 4 HR.	K-PEN-G 12 HR.	PROC. PEN. 12 HR.
Nasopharyngitis	37	44	25
Otitis media	23	25	13
Tonsillitis	12	14	26
Bronchitis	12	12	13
Pneumonia	3	4	5
Skin infections	4	6	11
Lymphadenitis	0	4	12
Miscellaneous	0	2*	1†
Total infections	91	111	106

*One case each of herpetic stomatitis and infected thyroglossal cyst.
†Gonococcal vulvovaginitis.

Table II lists the number of patients in each of the programs on the basis of their infections. The distribution of the various diseases was, in general, similar among the three groups.

Except for fifty-two cases all of the patients were noted to have fever during the initial visit. Those who had no fever were found to have other indications for antibacterial therapy, such as suppurative otitis media, pyodermia,

lymphadenitis, chronic pulmonary infection, and recurrent respiratory infections, which failed to improve without antibacterial treatment. The distribution of the afebrile cases was comparable in all groups.

CLINICAL AND LABORATORY RESULTS

The duration of treatment ranged from two to fourteen days, with an average of four to five days. The clinical responses to therapy are tabulated in Table III. When there were rapid defervescence and subsidence of clinical manifestations of the disease, the response to therapy was considered to be good. Equally satisfactory improvement was observed in patients treated at intervals of four or twelve hours. Further, the patients who received procaine penicillin responded as well as those who received potassium penicillin-G. The patients who showed poor response to penicillin frequently harbored penicillin-resistant bacteria, or presumably had a viral infection. However, only thirteen of the thirty-nine patients who responded poorly to penicillin required additional antimicrobial treatment.

Very few untoward reactions ascribable to penicillin were noted in the 292 patients treated. This observation is of interest since approximately 70 per cent of these patients had previously received penicillin for the treatment of other infections. Two patients developed skin eruptions during treatment, which were papular and erythematous but not urticarial in character. No evidence of irritation of the buccal or lingual mucosa was noted. No patient developed moniliasis. A few patients developed nausea or mild diarrhea during treatment. Thus, very few patients showed any untoward reaction to orally administered penicillin and in no instance was the reaction serious.

Serum penicillin levels were determined in 288 of the 292 patients who received orally administered penicillin. The data are summarized in Table IV. Penicillin levels above 0.03 unit per milliliter, the commonly accepted minimum concentration necessary to inhibit the growth of penicillin-susceptible bacteria, were maintained for at least two hours under the four-hour program and for two to four hours under the twelve-hour program with potassium penicillin-G. The serum penicillin levels resulting from the administration of procaine penicillin were somewhat lower at one-half to two-hour intervals than were those obtained after the administration of similar amounts of potassium penicillin-G. About 50 per cent of the samples of serum obtained at two- to four-hour intervals following the oral administration of procaine penicillin and 30 per cent of the corresponding samples of serum obtained following the administration of potassium penicil-

TABLE III. CLINICAL RESPONSE ACCORDING TO DOSAGE REGIMEN

	DOSAGE REGIMEN					
	K-PEN-G 4 HR.		K-PEN-G 12 HR.		PROC. PEN. 12 HR.	
RESPONSE	NO. OF CASES	%	NO. OF CASES	%	NO. OF CASES	%
Good	81	89	99	91	89	84
Doubtful	10	11	12	9	17	16
Total	91	--	111	--	106	--

lin-G were less than 0.03 unit per milliliter.

Bacteriologic studies were performed on 288 patients whose sites of infection permitted the obtaining of material for cultures. Similar cultural studies were repeated during the course of therapy. The comparative data of the pretreatment and treatment phase cultures are shown in Table V. It is recognized that the isolation of a pathogenic bacterium from the throat or nasopharynx of a patient with a respiratory infection does not establish the bacterium as the causative agent. The reduction of these bacteria during the course of treatment can, however, be significant. In those instances when there is concomitant reduction or disappearance of pathogenic bacteria and rapid subsidence of clinical manifestations, a cause-and-effect relationship can be postulated.

It will be noted that penicillin-susceptible species were reduced in a comparable manner in each of the treated groups. Reduction of penicillin-resist-

TABLE IV. SERUM PENICILLIN LEVELS ACCORDING TO DOSAGE REGIMEN

DOSAGE REGIMEN	SERUM PENICILLIN LEVEL, U./ML.	INTERVALS FOLLOWING A DOSE		
		½-2 HR.	2-4 HR.	4-6 HR.
K-Pen-G 4 hr.	Mean	0.12	0.05	–
	Median	0.06	0.015	–
	Range	< 0.015–0.05	< 0.015–0.5	–
	No. of tests	19	32	–
	% assayable	84	60	–
K-Pen-G 12 hr.	Mean	0.45	0.12	0.04
	Median	0.25	0.06	< 0.03
	Range	< 0.015–4.0	< 0.015–0.5	< 0.03–0.125
	No. of tests	43	60	23
	% assayable	91	70	44
Proc. Pen. 12 hr.	Mean	0.19	0.11	0.013
	Median	0.06	0.03	< 0.06
	Range	< 0.015–2.0	< 0.015–1.0	< 0.015–0.06
	No. of tests	35	70	6
	% assayable	83	70	50

TABLE V. COMPARISON OF THE PRETREATMENT AND TREATMENT PHASE BACTERIAL CULTURES ACCORDING TO DOSAGE REGIMEN

BACTERIAL SPECIES	K-PEN-G 4 HR.			K-PEN-G 12 HR.			PROC. PEN. 12 HR.		
	POSITIVE*	NEG. OR REDUCED†		POSITIVE	NEG. OR REDUCED		POSITIVE	NEG. OR REDUCED	
	NO.	NO.	%	NO.	NO.	%	NO.	NO.	%
Penicillin susceptible									
Pneumococci	49	40	82	61	42	69	44	32	73
H. streptococcus	14	12	86	4	4	100	12	10	83
Staph. aureus, coag. pos.	9	8	90	24	20	83	16	15	94
Total	72	60	83	89	66	74	72	57	79
Penicillin resistant									
H. influenzae	33	16	48.5	18	9	50	16	11	69
Staph. aureus, coag. pos.	7	2	28	5	0	0	5	1	20
Total	40	18	45	23	9	39	21	12	57

*Number of pretreatment cultures containing the indicated species.

†Number of treatment phase cultures in whch the indicated species were either absent or their number had been significantly reduced in comparison with the pretreatment culture.

ant species occurred less frequently in all the groups. An average of 78 per cent of the penicillin-susceptible species in contrast to 47 per cent of the penicillin-resistant species were reduced in the subsequent cultures during the course of treatment.

DISCUSSION

The primary purpose of this study was to determine whether penicillin administered orally, in the same daily dose, was more effective when prescribed at intervals of four hours or of twelve hours. A secondary purpose of the investigation was to determine whether potassium penicillin-G and procaine penicillin had comparable effects when administered at intervals of twelve hours.

The data indicate that the groups of patients under study were, by statistical analysis, comparable in every respect except for minor differences in age distribution. The observed differences in age distribution are not thought to have had a significant influence in the observed results.

The effectiveness of penicillin was judged clinically by observing the changes in the subjective and objective manifestations of the various infections. Comparison of bacterial cultures obtained prior to and during treatment served as a second measure for evaluating the effectiveness of treatment.

The results indicate that equally satisfactory improvement was observed regardless of the schedule of administration or type of penicillin preparation employed as a therapeutic agent.

It will be noted that the mean one-half- to two-hour serum penicillin levels described in Table IV exceed bactericidal levels for most strains of pneumococci, β hemolytic streptococci, and penicillin-susceptible staphylococci. These three bacterial species were found in the majority of the patients from whom pathogenic penicillin-susceptible bacteria were isolated as shown in Table V.

The results described indicate that a twelve-hour interval between doses of orally administered penicillin does not reduce the effectiveness of the drug in combating moderately severe infections. Such a program of treatment, however, is not advocated for severe infections.

SUMMARY

A series of 308 cases of common infections in infants and children was studied to evaluate the effectiveness of penicillin administered orally at intervals of four and twelve hours.

Patients who received 300,000 units of penicillin at intervals of twelve hours responded as satisfactorily as did those who received 200,000 units as the initial dose followed by 100,000 units at intervals of four hours.

The effectiveness of procaine penicillin was comparable to that of potassium penicillin-G, when each was administered in equivalent amounts at intervals of twelve hours.

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CHRONIC MYELOGENOUS LEUKEMIA IN CHILDREN

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CHRONIC myelogenous leukemia, the commonest form of the disease in adult life, is relatively uncommon in childhood, although isolated cases have been recorded from time to time even in infancy. No attempt has been made to collect all of these published cases, although Eisenberg and Wallenstein[1] in 1934 in reporting a case state that they found only thirty others in the literature. Poncher, Weir, Limarzi[2] in 1942 found only two previously reported authentic cases in infancy (6 months and 15 months) in addition to the one they observed at 6 weeks of age, while Keith[3] recorded an infant with onset at 3 months of age. Because of the infrequency of its occurrence, it was thought of interest to report fifteen cases of chronic myelogenous leukemia that have come under my observation in St. Louis and to review certain interesting features of the disease and its treatment in childhood.

The fifteen patients were seen in a twenty-year period (1931 to 1950) with the exception of one in 1927. The incidence of the chronic form in children has been about 5 per cent of the 294 children with leukemia during the same time, the others being acute leukemia. These were eleven boys and four girls which in spite of the small size of the group is a more striking predominance of males (3:1) than noted in acute leukemia in children (3:2).[4] One child was a Negro. At the time of apparent onset, six of the patients were infants, three in the first year, two in the second, and one 26 months old, while the remaining nine were from 4 to 12 years of age. Only four were from the St. Louis area, five being from Illinois, three from Indiana, two from Oklahoma, and one from Kentucky. In Table I are summarized certain features in the children of this group including the time of onset, duration, type of therapy, and terminal symptoms—all of which will be briefly discussed later. The sequence in the tabulation is based on the age at apparent onset of the disease.

The diagnosis of chronic myelogenous leukemia in every case was based on a hyperleukocytosis with predominant granular cells, including younger forms such as myelocytes and metamyelocytes, and great enlargement of the spleen. The relatively long duration of the disease, together with the absence of peripheral glandular enlargement and early acute toxic symptoms were believed to exclude acute myelogenous leukemia. While the thrombocytopenia and hemorrhages present in the youngest patients might suggest acute leukemia, the single patient (Case 6) in this group in whom the disease was of shorter duration had characteristic findings of chronic myelogenous leukemia at necropsy.

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In Table II is shown a characteristic blood examination on each patient, and all other blood examinations were of the same general pattern. The single exception is one patient (Case 14) who was not seen until a terminal change to an acute leukemic picture.

For descriptive purposes, the cases will be divided into four groups in each of which certain characteristics are similar. They include (1) infants, and older children (2) with little or no planned therapy, (3) with well-planned x-ray treatment, and (4) with therapy by other agents (urethane and P^{32}). In the abstracts of the individual cases, only brief summaries will be given with the essential features stated as concisely as possible. Some patients could not be followed as closely as others chiefly because they lived at distant points, and their records are correspondingly incomplete.

TABLE I. SUMMARY OF DATA ON FIFTEEN CHILDREN WITH CHRONIC MYELOGENOUS LEUKEMIA

NO.	NAME	SEX	AGE OF ONSET	YEAR AND AGE WHEN FIRST SEEN	TOTAL DURATION	TYPE TREATMENT	TERMINAL SYMPTOMS
1	P. R.	M	3 mo.	1936, 15 mo.	15 mo.	Transfusion	Acute hemorrhagic
2	J. R.	F	3 mo.	1940, 4 mo.	11 mo.	Transfusion	"Cerebral hemorrhage"
3	L. L.	F	8 mo.	1943, 17 mo.	9 mo.	Transfusion	Pneumonia. Died during transfusion
4	R. S.	M	13 mo.	1949, 13 mo.	3+ yr.	Transfusion and x-ray	Still living
5	C. F.	M	19 mo.	1946, 21 mo.	8 mo.	None	?
6	L. K.	M	26 mo.	1950, 27 mo.	3 mo.	None	Acute hemorrhagic (autopsy)
7	J. H.	M	4 yr.	1934, 4 yr.	1½ yr.	X-ray	Hemorrhages (leukopenia)
8	H. J.	M	5½ yr.	1936, 5¾ yr.	4¼ yr.	X-ray	Toxemia, fever
9	E. C.	F	8 yr.	1927, 9 yr.	2 yr.	None	Acute hemorrhagic
10	E. H.	M	8 yr.	1931, 8½ yr.	2 yr.	X-ray	Asthenia and anemia
11	R. F.	F	9 yr.	1944, 9 yr.	5½ yr.	X-ray	Toxemia, fever
12	D. L.	M	10 yr.	1945, 10 yr.	4½ yr.	X-ray	Toxemia, fever
13	J. P.	M	11 yr.	1932, 11 yr.	1 yr.	X-ray	?
14	R. T.	M	11 yr.	1947, 12½ yr.	1½ yr.	X-ray and urethane	Acute hemorrhagic
15	H. D.	M	12 yr.	1943, 13 yr.	2 yr.	P^{32}	Acute hemorrhagic

INFANTS

The principal characteristic of infants with the disease, in addition to hyperleukocytosis and splenomegaly, was a constant thrombocytopenia with special tendency to anemia and hemorrhage. Transfusions had a transient effect, but the hemorrhagic symptoms seemed difficult to control. In one instance they were fatal in three months, and four others lived only eight to fifteen months. Of special interest is one patient (Case 4) who is still living after three years, although he required very careful supervision and care during this time, which will be mentioned later. Some of the data on these children are summarized in Table I, the blood picture in Table II, and brief summaries follow.

CASE 1.—Preston R., a 15-month-old boy. The spleen had been noted to be very large at age 3 months; at that time the blood count was 210,000, and a diagnosis of chronic myelogenous leukemia was made. He had received transfusions and x-ray irradiation about once monthly with reduction in leukocytes and clinical improvement. He was admitted because of a bilateral detached retina and choroid thought

TABLE II. CHARACTERISTIC BLOOD PICTURE OF FIFTEEN CHILDREN WITH CHRONIC MYELOGENOUS LEUKEMIA

NO.	NAME	SEX	AGE	R.B.C. MILLIONS	HB. GM.	PLATELETS	TOTAL LEUKO-CYTES	BAS.	EOS.	BLASTS	MYELO-CYTES	JUV.	STAB.	SEG.	LYMPH.	MONO.
1	P. R.	M	15 mo.	2.5	7.8	Scanty	19,200			6	9	9	13	44	16	
2	J. R.	F	4 mo.	3.5	9.2	110,000	96,000	1	3	14	12	12	18	21	19	
3	L. L.	F	17 mo.	3.1	4.8	140,000	110,000	1		4	16	19	18	16	18	1
4	R. S.	M	13 mo.	3.5	9.1	39,000	146,000	1	2		11	6	22	28	30	
5	C. F.	M	21 mo.	3.6	12.1	115,000	72,000	2	5	9	7	5	9	37	12	4
6	L. K.	M	28 mo.	3.7	10.7	Decreased	187,000	3	2	6	16	15	15	29	10	4
7	J. H.	M	4 yr.	3.8	11.4	450,000	166,000	1	2	12	14	17	17	25	12	
8	H. J.	M	9 yr.	3.0	9.5	710,000	416,000			11	50	12	11	16		
9	E. C.	F	8 yr.	3.1	5.2	224,000	313,000		2	9	17	16	14	33	5	4
10	E. H.	M	8 yr.	2.3	9.4	620,000	440,000			5	45	10	11	20	4	5
11	R. F.	F	10 yr.	3.5	7.8	Abundant	410,000	4	6	12	16	16	24	21	1	
12	D. L.	M	10 yr.	3.1	11.5	1,500,000	54,000	1	1		22	13	25	24	10	4
13	J. P.	M	11 yr.	3.6	10.9	610,000	232,000			7	13	14	25	39	1	1
14	R. T.	M	12 yr.	1.2	2.3	28,000	69,000			95			1	3	1	
15	H. D.	M	12 yr.	2.0	6.4	515,000	488,000	5	4	5	22	27	20	14	1	2

to be due to leukemic ocular infiltration. The spleen and liver were much enlarged and firm. Peripheral blood showed 19,200 leukocytes with many young granular forms and decreased platelets (Table II) and numerous small skin hemorrhages. A total of 360 R units of x-ray was given to both orbital regions. The leukocytes decreased to 8,000 within a month with persistence of thrombocytopenia and more hemorrhages into the skin and mucous membranes which were partially controlled by transfusions. Death occurred about five weeks after discharge with acute hemorrhagic leukemic manifestations.

CASE 2.—Judith R., a 4-month-old infant. The spleen had been noted to be considerably enlarged one month earlier and had been increasing in size. She was happy and gaining, but the spleen was firm and extended below the umbilicus, and the liver was also enlarged. There was a moderate anemia (hemoglobin 6.9 Gm.), and the platelets were decreased. There were 96,000 leukocytes with many young granular cells (Table II). She was admitted several times during the next eight months and given blood transfusions. The thrombopenia persisted, and at times she had petechial skin hemorrhages, but she continued to gain and thrive. The enlarged spleen, leukocytosis, and myeloid blood picture persisted. Two months after her last hospital admission, she died at home from what was diagnosed as a cerebral hemorrhage at the age of 14 months.

CASE 3.—Linda L., a 17-month-old infant, had been noted to have a very large abdomen since 8 months of age which gradually increased in size. Since the age of one year, she had been able to take only small amounts of food and had become progressively paler but had had no hemorrhages. On examination, a huge firm spleen reached to the pelvic brim, and the leukocytes were 110,000 with many young granular cells and myelocytes (Table II). The hemoglobin was 4.8 Gm., and the platelets decreased. Temperature was 39.5° C., and there were signs of pneumonia at the right base. She was given three blood transfusions, and during the third transfusion, two days after admission, the child died. There was no necropsy.

CASE 4.—Ronine S. was first seen Aug. 5, 1949, at the age of 13 months (weight 25 pounds) because of epistaxis. He was said to have had a large abdomen since early infancy but had always been healthy. The spleen was firm and reached the pelvic brim, and the liver was 6 cm. below the costal margin. The blood showed a hyperleukocytosis with myelogenous picture and decreased platelets (Table II), and the tibial marrow was very hypercellular with hyperplasia of myeloid cells and marked increase in early forms. Erythroid elements appeared normal, but no megakaryocytes were seen. He was given x-ray therapy (25 R) over the spleen August 9, 11, 31, September 7, October 12, 13, 17, and 19 (50 R) with gradual reduction in total leukocytes to 18,600 on November 9, although the spleen still extended below the umbilicus. In October and November he was given 1,250 c.c. of blood for anemia.

During the next two years (1950 and 1951) he was seen several times each month in the clinic and had eight hospital admissions. Much of the time he was ambulant, and his symptoms were chiefly those due to recurring anemia. At times he had mild upper respiratory infections which responded well to antibiotic therapy. During the summer months he suffered from periods of moderately high fever which were apparently associated with the hot weather and with an inability to perspire. The platelets have always been greatly decreased, and many nosebleeds occurred but only occasionally were severe. On one occasion he had much bleeding from the intestinal tract and on another a large cephalhematoma from a fall. Transfusions were given when the hemoglo-

bin fell to 7 Gm. or below, and a total of 4,500 c.c. of blood was administered in 1950 and 5,000 c.c. in the first seven months of 1951. After July, 1951, the tendency to develop anemia was definitely less, and transfusion was required only once (750 c.c. in January, 1952) with maintenance of hemoglobin values to 11 to 12 Gm. The total leukocytes have usually varied between 10,000 and 40,000 with only occasional readings of 60,000 to 80,000. The differential count always showed some myelocytes and other young granular forms but not in large numbers and definitely less (around 10 per cent) after the second year of the disease (1952). Several marrow examinations have given a picture of myeloid hyperplasia similar to that done initially. The spleen has remained very large and firm, reaching the pelvis.

After the first course of x-ray therapy, irradiation over the spleen (50 R) was given on three occasions in January, 1950, without effect on the spleen size but with some reduction in total leukocytes. In March, 1951, because of a persistent cough and radiographic evidence of pulmonary infiltration at the hilum and some diffuse parenchymatous infiltration thought possibly leukemic, he was given additional x-ray. This consisted of 450 R to the chest and 350 R over the spleen in divided doses over a three-week period. Following this, he developed a leukopenia of 3,000 to 7,000, lasting three months, and during this time received 3,500 c.c. of blood for persisting anemia. The spleen remained large, but his general condition was much improved after this, and anemia has recurred only once with transfusion in January, 1952. During 1952, his general condition was distinctly better than previously, erythrocytes being maintained at over 4 million and the hemoglobin 10 to 12 Gm. The leukocytes were 10,000 to 20,000 with only a small percentage of young granular cells. Although the spleen remained large and the platelets low, he had no evidence of hemorrhage. His weight at age 4 was 40 pounds and his condition excellent. A marrow examination at this time showed a moderate myeloid hyperplasia but good erythropoiesis and young megakaryocytes.

CASE 5.—Charles F. had previously been a healthy boy but had developed an otitis media at 19 months and was found to have a hyperleukocytosis of 72,000 with an enlarged liver and spleen. When examined at age 21 months, the only notable physical findings were firm spleen and liver about 2 inches below the costal margin. The peripheral blood picture is shown in Table II. A tibial puncture showed a marked hyperplasia of granular elements of the marrow. No information on his subsequent course was obtainable except that the child died six months later.

CASE 6.—Leslie K. was seen at 28 months of age with the history that one month previously when seen for acute otitis media, he was found to have a hyperleukocytosis. When examined, there were no symptoms but a large firm spleen which reached below the umbilicus, and there was an enlarged liver and a leukocytosis of 120,000 with typical chronic myeloid picture (Table II). A marrow puncture showed striking myeloid hyperplasia. No treatment was thought to be indicated since he had only moderate anemia and no hemorrhages, although the platelets were somewhat decreased. He did well subsequently, although the hyperleukocytosis and enlarged spleen persisted, but rather suddenly three months later he had severe epistaxis with vomiting of blood clots, and when admitted to the hospital the following day was found to be dyspneic and lethargic with hemoglobin of 4.7 Gm., bleeding from the mucous membranes and into the skin. Before transfusions could be given, he coughed, choked, and expired three hours after admission. Leukocytes were 240,000. Necropsy showed extensive skin and visceral hemorrhages with typical chronic myelogenous leukemic infiltration of the organs and marrow.

One patient (Case 4) may be commented on briefly because he has survived the period of severe thrombopenic hemorrhagic danger during infancy in which the others died. For two years after the apparent onset at 13 months of age, he continued to have hemorrhages and recurring anemia for which he received more than 10,000 c.c. of blood by transfusion. Through the third year of the disease the tendency to hyperleukocytosis, hemorrhage, and anemia has markedly diminished, although thrombocytopenia and splenomegaly persist. Whether x-ray irradiation given previous to the onset of this "remission" was a factor or whether he has survived beyond the age at which bleeding and anemia dominate the picture cannot be stated. It is certain that his survival is a result of close supervision and care and illustrates the fact that certain patients may be carried through this early period.

OLDER CHILDREN WITHOUT CAREFULLY SUPERVISED TREATMENT

The four children in this group were either given no treatment or received x-ray irradiation on several occasions because of hyperleukocytosis. Since they were not under close medical supervision and observation and their treatment was somewhat casual, they may be considered a control group to illustrate the usual course of the disease under such circumstances. Their records are incomplete, but the duration of the disease was one to two years. Two of the children had terminal hemorrhagic symptoms; one was said to have become asthenic and anemic before death, and in the other no information about the later symptoms could be obtained.

CASE 7.—John H., a 4-year-old boy whose blood count had been normal in April, 1934, and who had no complaints, was found to have a hyperleukocytosis of 120,000 seven months later. When admitted for examination in December, 1934, the spleen and liver were only slightly enlarged, and there were no symptoms. The leukocytes were 166,000 with typical chronic myeloid blood picture but without anemia or thrombocytopenia (Table II). He was given x-ray therapy (total 100 R body irradiation on four days) with fall in leukocytes to 16,000 four days after the last irradiation. He was not seen by me again but received additional irradiation over the splenic area at home and remained in relatively good physical condition with total leukocytes at a relatively low level for about eighteen months. During this time, he received several transfusions, and during the latter weeks of his life he had moderately severe hemorrhagic symptoms with bleeding from the nasal and oral mucous membranes. He died following a transfusion.

CASE 9.—Edith C. In December, 1926, one year before admission, she had had an attack of high fever with pain and swelling of the extremities lasting several weeks. One month later the abdomen was noted to be large, and the blood count showed a leukemic blood picture. She had been anemic and was dyspneic on exertion. On examination (October, 1927) at age 9, she had a considerably enlarged heart with loud transmitted systolic murmur; she was pale (hemoglobin 5.2 Gm.) and emaciated. A large firm spleen reached the pelvic brim, and the leukocytes were 313,000 (Table II). Transfusions were given for the anemia but no other therapy. She was not seen again but died a year later. During the latter part of her illness, she was stated to have had frequent nosebleeds and considerable bleeding from the gums.

CASE 10.—Elgyn H. was first seen (1931) at the age of 8 years because of an enlarged abdomen. He had had no symptoms except that he had seemed to fatigue easily for the past six months. On examination, a large firm spleen reached the pelvis and

extended 8.5 cm. to the right of the umbilicus. The leukocytes were 440,000 with many myelocytes and other young granular forms (Table II). Following x-ray therapy, the total leukocyte count fell to 9,800 within three weeks, and the spleen was much reduced in size but remained large. Two months later the count had risen to 55,000, but no further observations were possible. He died sixteen months later with terminal symptoms of anemia and asthenia, but no details were obtained.

CASE 13.—Jesse P., an 11-year-old Negro boy, was found to have a much enlarged firm spleen (August, 1932), reaching below the umbilicus, and a leukocyte count of 255,000 with a typical picture of chronic myeloid leukemia. He had no symptoms other than some abdominal discomfort. Following x-ray irradiation (October), his spleen was considerably reduced in size, and the leukocytes fell within three weeks to 34,000. Six months later (March) the count had risen again to 500,000 with no symptoms other than discomfort from a large spleen which reached the pelvic brim. An additional course of x-ray irradiation in May produced a reduction in the count to 60,000 within two weeks with impovement in his general condition. He had no anemia or hemorrhages during the periods of observation. The boy was reported to have died suddenly three months later, one year after having been first seen.

OLDER CHILDREN WITH CAREFULLY SUPERVISED X-RAY IRRADIATION THERAPY

The three children in this group were almost identical in their course, response to therapy, and terminal symptoms. All had initial hyperleukocytosis and splenomegaly without other symptoms. In therapy, the hyperleukocytosis was disregarded, and treatment by x-ray irradiation over the splenic area was given only when the splenic enlargement became so great as to produce evident pressure symptoms. These were inability to ingest more than small amounts of food, weight loss, some gastric distress, and occasionally vomiting. Usually a year or more elapsed after the diagnosis was made before any therapy was given. In the first x-ray treatments usually less irradiation was necessary to produce relief of symptoms and reduction in spleen size, and the remission lasted longer than later, and always a striking decrease in total leukocytes occurred. A return of hyperleukocytosis and splenomegaly with pressure symptoms after some months or longer always developed and again responded to x-ray. This procedure was continued for two to three years, and during the intervals the patients were clinically in excellent condition and able to carry on all normal childhood activities. The total duration of the disease in these patients was four to five and one-half years.

The terminal manifestations were quite similar in each child. In the fifth or sixth year of the disease severe pains in the legs and thighs developed and persisted with only slight temporary remissions; no lesion could be found except varying degrees of bone rarefaction in roentgenograms. Within a few weeks severe toxicity, asthenia, and fever appeared and continued until death about a month later. Fever was of the septic type, but no evidence of pulmonary or other infection was found, and blood cultures were negative. The blood continued to show the picture of chronic myelogenous leukemia. Summaries of these three cases follow.

CASE 8.—Henry J. was first seen by me in June, 1936, with no symptoms

except a very large spleen and hyperleukocytosis with differential count typical of chronic myeloid leukemia. During the next two years, he remained well, active, and in school regularly, and during this time was given splenic irradiation with x-ray by his physician. He came under my care in July, 1938, because of several attacks of epistaxis, and a blood examination showed 810,000 leukocytes, all granular cells with somewhat scanty platelets (Table II). The spleen filled the entire abdomen except the right upper quadrant. A series of x-ray irradiation (four times 60 R) in a week was followed by a reduction in leukocytes to 100,000 within two weeks and platelet count of 800,000 with spleen much reduced but still reaching the umbilicus. General clinical condition remained excellent following treatment.

The same sequence recurred every six months for two years. Gradual increase of hyperleukocytosis with huge spleen, loss of appetite and pep, and x-ray therapy was followed by reduction in leukocytes and spleen size with return to normal activity and apparent health in the intervals. Irradiations were given in January and June, 1939, and in January and June, 1940. During the early part of 1940, pain in the lower extremities occurred, at times lasting several days without physical findings, and x-rays revealed numerous patchy areas of rarefaction in bones of thighs and legs. The pains were relieved by the irradiation in June, 1940, but in August, 1940, he developed fever, anorexia, asthenia, and dyspnea. The fever was of a swinging septic type, but blood cultures were sterile. Orthopnea persisted; the spleen was tremendous, and the leukocytes around 200,000 with the same myelogenous picture, except that young granular cells predominated, and there were many myeloblasts. There was no bleeding. In spite of transfusions and sulfa therapy, the symptoms persisted, and the boy died Sept. 11, 1940, more than four years after being first seen.

CASE 11.—Rose F., a 9-year-old girl, was first diagnosed in July, 1944, and followed until her death five and one-half years later. The disease was first recognized because of an enlarged spleen, by a blood examination which showed a hyperleukocytosis of 308,000 with typical granular myeloid leukemic cells. There were no symptoms, and the abnormal physical findings were limited to the large firm spleen which reached the umbilicus, and the leukemic blood picture. Because she was very active physically and had no complaints except that she was moderately thin and did not gain weight, it was decided to give no therapy. For the next two years she remained physically well, although the leukocytes remained high (Table II), and the spleen continued to enlarge until it occupied the entire left abdomen and the right lower quadrant, so that only small quantities of food could be taken. For this reason, she was given two doses of 75 R each over the spleen in June, 1946. Two weeks later the leukocytes were 54,000, and after a month the spleen was only slightly below the costal margin. The continued improvement in her general condition was striking, and a year later she weighed 80 pounds, a gain of 29 pounds, and had been active, healthy, and without complaint. When examined in July, 1947, after fracturing her forearm in a fall from a swing, the spleen was again found to be slightly below the umbilicus, and the leukocyte count was 240,000. It was not until October, 1947, sixteen months after the first therapy, that the spleen had again become so large as to produce discomfort by encroaching on the other abdominal organs, and a second course of x-ray was given. At this time a total of 375 R was given with later decrease in spleen size but only to the level of the umbilicus, a decrease in total leukocytes, and marked increase in comfort and well-being. A similar recurrence of huge splenic enlargement with accompanying pressure symptoms required a third and fourth course of x-ray therapy in July, 1948,

and in June, 1949. Although the leukocyte count remained between 100,000 and 300,000 except for a few weeks after x-ray irradiation, the child remained in excellent condition, attended school regularly, and participated in all normal activities.

The terminal phase of the disease began in October, 1949, four months after the last therapy and more than five years after the onset of the disease. Moderately severe pain developed in the left hip and interfered with walking. An x-ray showed extensive and diffuse honeycombed appearance of all pelvic bones and femur with scattered small rarefaction and loss of finer trabeculation (Fig. 1), changes considered due to a diffuse leukemic process in the bone with absorption of calcium. Some local irradiation to the thigh was given in an attempt to relieve the pain, but in a few days listlessness and fever developed; the leukocytes rose to over 600,000, and anemia required a blood transfusion. A total of 3 mc. of P^{32} was given without effect. Moderate fever, hyperleukocytosis, asthenia, marked apprehension, difficult respirations, and toxicity continued, and the child died Nov. 21, 1949. The lungs were clear, and there was no evidence of infection.

Fig. 1.—Chronic myelogenous leukemic infiltration of pelvis and femora in Case 11.

CASE 12.—Daniel L. was first seen in December, 1945, at 10 years of age. On examination for an upper respiratory infection, he was found to have a slightly enlarged firm spleen extending 2 cm. below the costal margin. A blood count gave 54,000 leukocytes with a picture of chronic myelogenous leukemia (Table II) and bone marrow which was very cellular with large sheets of granular myeloid cells. There were no symptoms, and he remained in excellent general health with leukocytes around 100,000 and a gradually enlarging spleen. Ten months later (September, 1946) the leukocytes were 240,000 with the same type of differential, and a firm spleen reached be-

TABLE III. EFFECT OF X-RAY THERAPY ON LEUKOCYTES AND HEMOGLOBIN

Case 8

DATE	HEMOGLOBIN GM.	R.B.C. MILLIONS	LEUKOCYTES	THERAPY ROENTGENS	DATE	HEMOGLOBIN GM.	R.B.C. MILLIONS	LEUKOCYTES	THERAPY ROENTGENS
1-3-39	8.0	2.80	439,000	60	1-6-40	4.8	0.94	500,000	50
5			360,000	60	9			400,000	50
7			250,000	60	12	8.0	3.2	210,000	
10			150,000	60	18	9.0	3.2	120,000	
12			75,000		27	10.0	3.9	164,000	
28	11.0	4.06	66,000		2-5	10.7	4.0	184,000	50
2-11	11.5	4.40	18,000		10			160,000	50
					17	10.8	4.0	46,000	
					3-2	11.0	4.0	50,000	

Case 12

DATE	HEMO-GLOBIN GM.	LEUKO-CYTES	THERAPY ROENTGENS	DATE	HEMO-GLOBIN GM.	LEUKO-CYTES	THERAPY ROENTGENS	DATE	HEMO-GLOBIN GM.	LEUKO-CYTES	THERAPY ROENTGENS
9-19-46	7.5	240,000	100	2-23-48	8.5	300,000	200	4-4-49	9.1	189,000	100
28	7.5	183,000	75	28		200,000	200	6	9.3	106,000	100
10-12	9.5	112,000	150	3-6	9.7	123,000	200	8	9.6	57,000	100
19	9.6	93,000	75	30	10.7	125,000	200	11	9.3	41,500	100
11-10	11.1	54,000		4-3	13.1	44,300		13	11.6	25,900	

low the umbilicus. Because of increasing gastric distress with occasional vomiting, four x-ray irradiations over the spleen were given at weekly intervals, totaling 400 R, with fall in leukocytes to 33,000, decrease in spleen size to 3 cm. below the costal margin, and return to apparent good health. General condition remained excellent for sixteen months until February, 1948, when he developed loss of appetite and weight with spleen reaching well below the umbilicus and leukocyte count of 300,000. A second series of irradiations over the spleen, totaling 800 R, was given during February and March, 1948, with similar reduction in spleen and leukocytes, and clinical improvement, and a third course (450 R) of x-ray was given in January and February, 1949, with the same result except that the spleen decreased less and remained at the level of the umbilicus. Within a month the leukocytes had risen again to over 400,000; the spleen was much larger, and an unexplained fever of 39° to 40° C. developed with moderately severe anemia (hemoglobin 5.1 Gm.). He was transfused, and following a fourth course of x-ray (400 R in one week) over the spleen in April, 1949, his fever disappeared; the leukocytes fell to 25,000, and he was clinically improved. During the following month because of recurrence of fever and leukocytosis, and severe pains in the thighs and legs he was given additional x-ray irradiation over a period of four weeks, totaling 850 R, with only slight improvement.

The final phase of the disease became accentuated during June, 1949, with persistent irregular fever of 39° to 40° C., progressive asthenia, anorexia, apprehension, periods of profuse perspiration, and severe pain in the chest and legs. The spleen was extremely large, and the leukocytes ranged from 60,000 to 200,000 with a large proportion of the cells being myelocytes. There was no severe anemia (hemoglobin 10 to 11 Gm.), but the platelets were decreased, and a few small hemorrhages developed on the legs. A blood culture was negative, and the chest was clear on fluoroscopic examination. Although he appeared septic and toxic, the symptoms seemed a result of the disease and not from infection. Death occurred July 4, 1949, four and one-half years after the first symptoms were noted.

One feature of considerable interest in x-ray therapy in these children concerns the relatively rapid rise in hemoglobin and erythrocyte readings coincident with the fall in total leukocytes during and immediately after irradiation. In Table III are shown the blood counts and hemoglobin associated with five periods of x-ray treatment in two of these children. The appearance of a prompt rise in hemoglobin and erythrocytes after the decrease in leukocytes is evident and in some instances striking. While this increase is somewhat more rapid than that often seen in erythrocytic regeneration, it is difficult to offer any other explanation. The anemia accompanying hyperleukocytosis is not a true erythrogenic aplasia but results from a suppression of erythrogenic activity from excessive myelocytic marrow hyperplasia. With irradiation, not only are the circulating leukocytes destroyed, but also the marrow granulopoiesis is so greatly reduced that its myelophthistic action on erythrocyte formation no longer operates. With the reduction of this "crowding" effect, erythropoiesis proceeds at a rapid rate and with prompt increase in erythrocytes in the circulating blood. Unfortunately, in the observations cited in Table III, no reticulocyte counts were done.

CHILDREN TREATED WITH URETHANE AND P^{32}

Only two children were treated with agents other than x-ray. One child in the second year of the disease received urethane therapy for a period of six months with reduction in leukocyte count but then developed severe anemia, thrombocytopenia, hemor-

rhage, and a blood picture of typical acute leukemia with death a few weeks later. The second child, six months after the diagnosis was first made, was treated with radioactive phosphorus (P^{32}) for six months, and after a two-month interval for an additional three months with little effect on the hyperleukocytosis and splenomegaly. At the end of this time he developed severe hemorrhagic manifestations with thombocytopenia and died in a few weeks. As compared with the course of the other children reported, it was apparent that therapy with these agents was without benefit, and it appeared likely that the duration of the disease was considerably shortened. Brief summaries of these two children follow.

CASE 14.—Ronald T., a 12-year-old boy, had been found to have a much enlarged spleen and hyperleukocytosis of 680,000 one and a half years previously, with differential count typical of chronic myeloid leukemia. With x-ray irradiation, the leukocyte count fell to 4,000 but again rose, and he was given another course of x-ray irradiation with reduction in leukocyte count. Six months before being seen by me, although he was said to have been in excellent general condition, he was given urethane because of the persisting high leukocyte count. The initial dosage was 3 Gm. daily by mouth, starting in May, 1947, for ten days and continued in doses of 0.5 to 1 Gm. daily thereafter. The total leukocytes decreased within a few weeks to 8,000 but continued from 30,000 to 50,000 with little variation in the differential count and without anemia or other symptoms. His general condition remained good until early in November, 1947, when he developed a severe anemia for which he received a transfusion. Anemia and asthenia progressed rapidly, and when first seen by me on November 17, there was a severe anemia and thrombocytopenia (Table II) with 69,000 leukocytes most of which were young blast forms. He had a large firm spleen which extended to the midline and 2 cm. below the umbilicus, moderately enlarged and firm cervical, axillary, and inguinal lymph nodes, petechial skin hemorrhages, and bleeding gums. A sternal puncture done the following day showed little evidence of erythropoiesis and very scanty granular cells with large sheets of blast cells. The blood and marrow pictures as well as the clinical findings were typical of acute leukemia. He was given a blood transfusion with only slight benefit and died Nov. 29, 1947.

CASE 15.—Harry D., 13¾ years old, had had manifest abdominal enlargement with pallor for six months when first seen in October, 1943. The principal physical findings were a very large firm spleen reaching the pelvis, liver 5 cm. below the costal margin, and typical blood picture of chronic myeloid leukemia (Table II). The sternal marrow was very hyperplastic. He was treated with radioactive phosphorus (P^{32}) under the supervision of Dr. Carl V. Moore and Dr. Edward Reinhard, Department of Medicine, Washington University, in the manner that is usually effective in therapy of adults with the disease. This treatment was given from October, 1943, to February, 1944, and again from May to July, 1944. During this period, he remained in fairly good clinical condition, although the hyperleukocytosis and splenomegaly persisted. Rather abruptly in July, 1944, he developed extensive hemorrhages into the skin and had tarry stools and bloody urine followed by death in a few weeks. A few days before death the leukocytes were 105,000 with hemoglobin 7.0 Gm. and the same myeloid picture and no platelets seen in the blood smear. The conclusion was that the therapy with P^{32} had no arresting effect on the disease.

DISCUSSION

Although the group reported is small, the rarity of chronic myelogenous leukemia in childhood would

seem to render observations on a large series of cases difficult, and only a few general statements can be made from the limited material.

During infancy, the chief manifestations tend to be hemorrhagic, apparently due to a thrombocytopenia in which respect the disease differs from that in later life, and the bleeding tendency resembles that seen in acute leukemia. In most instances death occurs within a year or less, although it is occasionally possible with careful supervision and many transfusions to carry a patient along for a long period until the hemorrhagic tendency abates in spite of a persistence of the thrombocytopenia. In older children not under regular supervision and with little or no therapy, the duration of the disease was from one to two years, and in two children the terminal symptoms were of a hemorrhagic character. Before discussing the therapy used, brief comment will be made about certain features of the disease and the indications for treatment and its effect.

While the concept that leukemias are neoplastic in origin has wide acceptance, there are certain features that suggest the possibility of another mechanism in chronic myelogenous leukemia. The fact that apparently *all* granulopoietic tissue is involved simultaneously and that the process is essentially one of tremendous hyperactivity of normal development of granulocytes in the marrow has little in common with other neoplastic disease. The manifestations are primarily those due to the great excess of circulating leukocytes and their secondary infiltration of the organs, especially the spleen. The production and maturation of granular marrow elements is a normal physiologic process, and stimulation to increased activity is brought into play under various conditions, particularly in acute infections. The mechanism of this process and the production of the maturation stimulus (probably a hormone) which involves the entire bone marrow organ is entirely unknown, but the presence of such a maturation factor or substance in the production of leukocytosis seems certain. If one can assume that in chronic myelogenous leukemia, there is some anomaly whereby a persistent and continuous production of this maturation factor occurs with excessive granulopoiesis, the resulting changes would be exactly those observed in the disease. Eventually the marrow would become exhausted, or the excess of granular cells infiltrating various organs would produce changes incompatible with life.

Whatever the cause of the excessive marrow hyperplasia, all effective therapy has been based on the toxic destruction of the hyperplastic granulocytic cells, and the toxic agents used have included benzol, arsenic, urethane, and irradiation by x-ray and by radioactive phosphorus, all of which act primarily on the marrow itself. The effect of some of these agents is more difficult to control, and excessive toxic marrow injury may be produced by overtreatment. In children, x-ray irradiation appears to be more readily controlled and is quite effective. There is some evidence that the marrow cannot tolerate more than a certain amount of toxic injury by such therapeutic measures, and it would seem wise to limit their use so far as possible in order to prolong the period of effectiveness. For this reason it is advisable not to use such potent therapy simply to correct the hyperleukocytosis, but to reserve it for those

periods in which definite symptoms require relief.

In the group of children observed, this latter procedure was followed by the best results. The hyperleukocytosis was disregarded, and x-ray therapy in divided doses, controlled by its effect on the total leukocyte count, was given only when symptoms due to the enlarged spleen or to asthenia or other distress attributable to the disease occurred. These were always relieved and did not recur for a period of months. In later therapy more irradiation was usually required than initially. The terminal symptoms, which developed after four to five and a half years of essentially normal activity, were relatively acute and toxic in character. It is stated that at times resistance to one form of therapy develops, and another agent may be used successfully. In the three children mentioned, the development of the terminal toxic state was the first indication of any "resistance" to x-ray and too late for any effective change. In the two patients in whom treatment with urethane and with P^{32} was given, the response was much less satisfactory than those given x-ray, and by comparison, these two children reacted unfavorably, and the course of the disease may have been shortened by their use.

SUMMARY

Observations were reported on fifteen children with chronic myelogenous leukemia. During infancy the clinical manifestations were chiefly of a hemorrhagic character and associated with thrombocytopenia. In older children the disease was essentially the same as seen in adults. The best results in therapy were obtained by x-ray irradiation given at intervals and only for the control of disabling symptoms.

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MIST-O_2-GEN* THERAPY AND POSTURAL DRAINAGE FOR RESPIRATORY DIFFICULTIES OF THE NEWBORN INFANT

A Preliminary Report

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IN THE newborn infant, the treatment of respiratory insufficiency secondary to obstruction can be approached effectively. The purpose of this report is to present new techniques which have proved of real value in the therapeutic approach to those problems where obstruction is impeding adequate oxygen exchange.

RATIONALE OF CONTINUOUS OXYGEN-AEROSOL

The successful control of severe obstructive respiratory disease in infants and children by the use of Mist-O_2-Gen therapy has appeared in previous reports.[1, 2] Several pediatricians[3, 4, 5, 27] and otolaryngologists[6, 7, 8] advocate the use of controlled temperature combined with high humidity to maintain thin pulmonary secretions and reduce edema of the mucous membranes. The problem is to provide special air conditioning for these infants who require special climatic conditions.[9]

The rationale of aerosol therapy is based on the mechanical suspension of a high concentration of microscopic liquid particles in the inspired atmosphere.[10] By this method, the atmosphere within an enclosed space may be quickly saturated with water vapor. The further generation of nebulized fluids then causes the formation of an increasingly dense mist by which actual supersaturation is maintained. As ambient breathing draws this atmosphere into the bronchopulmonary tree, deposition of the suspended microscopic particles on the walls of the air passages results in water transfer to the mucous membranes throughout the lungs. Controlled particle size,[11] grossly consistent with that produced by standard nebulizers used for intermittent aerosol treatments, assures penetration of the minute droplets to the periphery of the respiratory tract.[10, 17] Liquefaction of desiccated secretions progresses from the trachea out to the prealveolar bronchioles.

APPARATUS

The Gordon Armstrong X4 portable baby incubator* has been accepted by the Armed Services for hospital use. This unit is simple in operation and relatively inexpensive. Using this incubator, we have designed the following appliances to better adapt the unit for "special air conditioning" and positioning of the newborn infant.

The written material which accompanies the Gordon Armstrong X4 incubator recounts oxygen concentrations of 65 and 70 vol. per cent within the enclosure at a flow of 4 to 6 liters per minute when both the top and bottom ventilators are closed. We

From the Pediatric Section, Medical Service, United States Air Force Hospital, Sheppard Air Force Base, Texas.

*This project was accomplished with equipment supplied by and parts reproduced with the permission of the Mist-O_2-Gen Equipment Division of the Production Foundry Co., 2700 Magnolia St., Oakland, Calif.

*Manufactured by the Gordon Armstrong Co., Inc., Cleveland, Ohio.

have been unable to reproduce this concentration with equipment as given on repeated trials. The results of a study on the performance of several models of incubators describe the importance of a tight enclosure to maintain adequate oxygen concentrations.[12] Reference to Fig. 1 will illustrate one method of securely closing the ventilator in the bottom of the incubator. From sheet aluminum of one-eighth inch thickness, a flat plate was constructed measuring 8 by 10 inches. The edges are beveled to allow the plate to slip between the sliding section of the ventilator grill and the bottom surface of the incubator. One edge of the plate is rolled to provide an angled surface for easy insertion or removal. When the greatest therapeutic concentrations of oxygen are needed for limited intervals, this procedure will allow concentrations of 85 vol. per cent to be maintained at 6 to 8 liters per minute oxygen flow. It has been demonstrated[13] that the administration of air of high oxygen content will change the irregular respiration of premature infants to a regular pattern. A therapeutic level of oxygen is one of the important factors in "air conditioning."

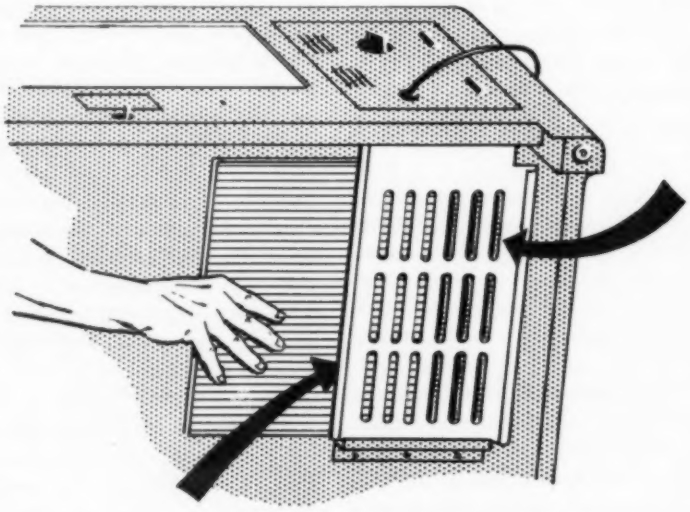

Fig. 1.—Bottom view of Gordon Armstrong incubator showing method of completely sealing ventilator grill.

POSTURAL DRAINAGE

When liquefaction of pulmonary secretions has taken place, elimination may still be deficient due to inadequate cough mechanism or ciliary action. To provide the assistance of gravity, the prone position on an inclined plane of about 15 degrees with the horizontal has been advocated.[14, 16] Ciliary action[15] may be twice as effective with the aid of gravity.

A support, measuring 13½ inches by 23½ inches, was made from one-sixteenth inch aluminum sheet stock (Fig. 3). One end was bent to form

a 3¾ inch vertical member. Covering this metal plate is a pad of foam rubber, one inch thick, to provide a firm but pliable surface. A second small pad of ½ inch foam rubber stands in a vertical position (Fig. 3) at the junction of the low end of the inclined plane and the end wall of the incubator. This pad cushions contact of the infant's head with the wall of the incubator when the inevitable "sliding down" occurs. Both foam rubber pads are enclosed in plastic slip covers to facilitate cleaning and to prevent moisture penetration. The circular cutout in the raised end of the support houses the body of the Mist-O_2-Gen nebulizer (Fig. 2).

The Mist-O_2-Gen nebulizer[2] (Fig. 2) is designed for continuous generation of large volumes of aerosol at oxygen flows of 4 to 8 liters per minute. The self-feeding design, constructed from cast aluminum and stainless steel, fitted over a glass jar reservoir, provides continuous operation over a period of eight hours and nebulizes approximately 350 c.c. of solution before refilling is necessary. The volume output of aerosol on 4 to 8 liters oxygen flow has been measured and exceeds that of standard nebulizers by 300 per cent. Eighty per cent of the nebulized particles are in the range between 1 to 3 microns.[11] During the past two years the reliable performance of the Mist-O_2-Gen nebulizer has been observed in several medical centers. The removable oxygen jet and liquid feed tube facilitate easy maintenance.[2]

METHOD

To prepare the Gordon Armstrong incubator for Mist-O_2-Gen therapy and postural drainage, the standard mattress is removed and the inclined plane and head cushion installed (Fig. 3). The oxygen hose is passed through the top ventilator grill using an enlarged end perforation nearest the heating unit at the end of the incubator. This adjustment allows the top to seal without obstruction. In those instances where optimum oxygen concentrations are needed for the initial few hours of treatment, the bottom ventilator grill is closed off as illustrated in Fig. 1. The Mist-O_2-Gen nebulizer is filled

Fig. 2.—Mist-O_2-Gen nebulizer during operation at 8 liters per minute oxygen flow. Eighty per cent of nebulized particles range between 1 and 3 microns.

with the prescribed solution and placed in the opening provided at the high end of the inclined plane where it will not interfere with care of the infant. The stream of oxygen-aerosol may be directed over the patient's head or to either side of the enclosure. When the temperature of the incubator has reached 85° F., the oxygen

Fig. 3.—Postural drainage unit and Mist-O_2-Gen nebulizer in Gordon Armstrong incubator. Oxygen feed tube enters incubator through enlarged slot in ventilator grill. Tape over ventilator control at base indicates that bottom ventilator is sealed shut to prevent oxygen leak.

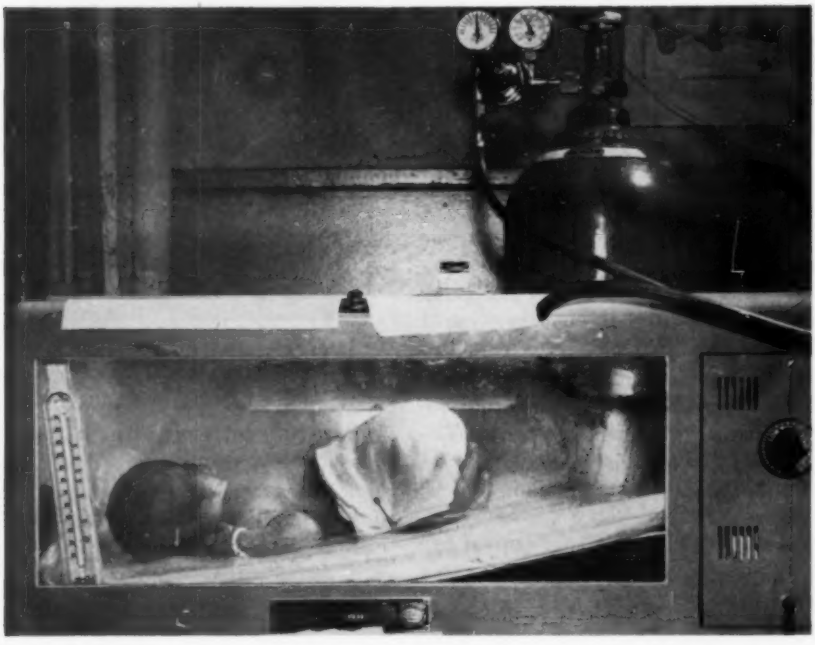

Fig. 4.—Aerosol concentration in incubator after 10 minutes' operation at 8 liters per minute oxygen flow.

flowmeter is opened to 8 liters per minute. Within four minutes the atmosphere is saturated, as shown by a reading of 100 per cent relative humidity (Serdex Laboratory Hygrometer). After this point, a cloud of aerosol mist collects in increasing density (Fig. 4), establishing and maintaining an oxygen-rich, supersaturated atmosphere. The unit is now ready to receive the patient.

COMPOSITION OF AEROSOL SOLUTIONS

Reports on techniques and apparatus for cold humidification[3, 4, 5, 9] describe the use of distilled water to increase the relative humidity in oxygen tents or draped cribs. Experience gained from both pediatric and adult patients treated with Mist-O_2-Gen therapy has demonstrated the value of solutions containing certain medicaments as reflected in more prompt clinical response. From the field of intermittent aerosol therapy, we have selected agents for both physical and pharmacological effects. Glycerin in low concentrations alters the vapor pressure of water solutions thereby prolonging the life period of the individual droplets.[17] Propylene glycol is also used to produce a stable and long-lasting aerosol. Evidence is reported[18] for the antibiotic activity of propylene glycol. Small concentrations of Neo-Synephrine* may be used to combat local edema.

Detergents added to aerosol solutions containing antibiotics possess the obvious advantages of detergency: emulsifying properties and reduced surface tension.[19] Among those detergents which have proved clinically valuable for this age group are the cationic detergent Zephiran* (alkyldimethylbenzyl ammonium chlorides in aqueous solution)[19, 20] and Triton-A-20* (alkyl aryl polyether alcohol).[21, 22] Gorman[8] reported dramatic results using Duponol-C† (sodium lauryl sulfate U.S.P.) in water vapor therapy for the treatment of laryngotracheobronchitis.

The rationale of the use of wetting agents in aerosol solutions for Mist-O_2-Gen therapy is based on two factors which appear to be active in these obstructive respiratory problems in the newborn infant. In those cases where foreign material (mucus, blood, amniotic fluid, or vernix) has formed a dessicated film lining the peripheral bronchial tree, the wetting action speeds liquefaction of this aspirated material. The emulsifying properties assist in breaking up mucus deposits. Atelectasis frequently persists after gross obstruction has been relieved. Wetting agents are known to reduce surface tension. Cohesion of moist surfaces of the air passages has been referred to[23] as one of the forces resisting aeration of atelectatic lung tissue. Evidence for this "sticking of moist surfaces" is found in the report of Berglund and Eder,[24] who performed thoracotomy in addition to applying positive pressure to relieve atelectasis. Objective proof of the importance of surface tension and evidence for the use of "surface-active substances" is presented in the report of Gruenwald.[25] The emulsifying properties of wetting agents are known to assist in loosening purulent exudates of high protein content. A relatively common finding in the lungs of infants who die in the neonatal period is the presence of hyaline or vernix

*Winthrop-Stearns, Inc., New York.

*Rohm & Haas Co., Philadelphia, Pa.
†E. I. du Pont de Nemours and Co.

membranes lining the alveolar ducts or alveoli. The significance of these membranes, which consist of the concentrated protein of aspirated amniotic fluid, in the production of neonatal atelectasis is indicated in a recent report.[26] It is reasonable to assume that the continuous deposition of a wetting agent on the surface of these membranes assists in their elimination by emulsification and by normal drainage mechanism.

In addition to the physical effects on cohesion of moist surfaces and the liquefaction of aspirated material, wetting agents are known to potentiate the antibiotic effect of penicillin and streptomycin. Not infrequently superimposed infection overweighs the obstructive factor.

The best results are realized by altering basic prescriptions for the individual patient. The composition of a solution may be changed during the clinical course. The basic prescription is written:

Glycerin	2.5%
Propylene glycol	2.5%
Neo-Synephrine	0.1%
Distilled water q.s.ad.	
	1,000 c.c.

The components may be varied when an increase in the density of the aerosol is required, i.e., glycerin 5 per cent and propylene glycol 5 per cent. Neo-Synephrine is often discontinued after the initial period of edema has subsided. Triton-A-20 is used in 0.1 per cent concentrations for the majority of cases and in 0.25 per cent when maximum wetting effect is indicated. For those cases of infection where penicillin-sensitive organisms are reported, 200,000 units of aqueous soluble penicillin per 100 c.c. is added to the aerosol solution. Streptomycin, although rarely indicated for this age group, has been used in concentrations of 50 mg. per 100 c.c. Because the Mist-O_2-Gen nebulizer delivers approximately one liter in twenty-four hours, prescriptions are written for this quantity to prevent waste.

SUMMARY

Mortality studies on the newborn infant indicate a high incidence from respiratory obstruction complicated by pneumonia. The rationale of the use of an oxygen-rich supersaturated atmosphere combined with postural drainage is discussed for the restoration of physiological drainage of the bronchopulmonary tree.

Mist-O_2-Gen therapy, a new apparatus for continuous aerosol treatment, is described together with the use of postural drainage during incubator care. Suggestions for the composition of aerosol solutions are presented. The apparent contribution of wetting agents in aerosol solutions to combat atelectasis appears to deserve further investigations.

The significance of liquefaction and elimination of bronchial and bronchiolar secretions and the topical administration of antibiotic agents in the control of neonatal respiratory death is indicated.

Cooperation of the Consulting Engineers from The Production Foundry Co., Oakland, Calif., was essential to this project.

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INTESTINAL RESECTION IN INFANTS

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PRIMARY intestinal resection in infants has long been considered a near fatal procedure.

In 1913, Dowd[3] recorded an instance of successful intestinal resection in an infant. After resection of the involved intestines for intussusception, he used a purse-string suture to invaginate each end of the resected gut, and followed this with a lateral anastomosis. Dowd also noted in his article a previous resection in 1912 by Hughes which utilized end-to-end anastomosis. Perrin and Lindsay,[11] in a monograph based on 400 cases of intussusception at the London Hospital in 1921, did not find a single child below the age of 3 years who survived resection. In 1945, Fallis and Warren[5] in their report of two cases of resection for irreducible intussusception mentioned that by 1921 Clubbe[2] could find but nineteen instances of survival following resection. Elliott-Smith[4] reported four cases in 1935, one of which was a spontaneous slough of the entire intussuscepted mass through the rectum, two of lateral anastomosis or short-circuit operations, and one of resection. All four of his reported patients survived. In 1939, Orr[10] recommended exteriorization procedures alone for gangrenous intussusception in infants. He felt immediate resection and anastomosis, at that time, was too elaborate an operation for the tolerance of the average infant. In his consideration of atresia of the intestine, Orr[10] felt that side-to-side procedures after the method of Ladd and Gross were most advisable. Wangensteen[13] in his excellent book on intestinal obstruction, in 1942, reported recovery of one infant, aged 4 months, following a stage resection.

The object of this short discussion is to present three infants, two of whom survived direct resection and intestinal anastomosis; the third did not.

CASE REPORTS

CASE 1.—Baby girl, No. 11381, aged 3 days, had a normal birth and was apparently a well-developed child upon delivery. On the second and third days the child vomited green meconium. Levine suction did not improve the child. Fluid balance was restored in so far as was possible prior to surgery and the child was operated upon in the third day of her life.

The lower third of the small bowel was atretic. The distal end of the jejunum ended in a blind pouch. Below this, there were few interrupted areas of distended bowel. Both ends of these segments were closed by atresia. The colon was present and apparently intact, but the right and transverse colon was suspended upon the same mesentery as the dilated portions of the jejunum and lower small bowel.

The lower isolated segments of gut were removed. An anastomosis was made with the lower end of the jejunum and the transverse colon. The proximal end of the right colon and appendix were removed. On the fifth day postoperatively, the child eviscerated in spite of retention sutures used at the time of the primary sur-

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gery. The infant was taken to surgery where the wound was re-closed. Twenty-four hours later the child expired.

CASE 2.—Baby boy, No. 35376. Apparently a normal delivery of a well-nourished child. On the second and third days the child began to vomit. Levine tube suction was put down but to no avail. An astute pediatrician noted milk curds in the stool during the first twenty-four hours of life. Efforts at hydration and to maintain a patent intestine by medical means met with failure.

At 6 days of age, the child's abdomen was explored. A malrotation of the intestines upon the mesenteric axis, with a mesenteric thrombosis incident thereto, was found. There was no ligament of Treitz, and the entire small bowel was suspended upon a mesentery anterior to the transverse colon. There was an early gangrene of a large portion of the small bowel.

Resection of over one-half of the small intestine was done with an end-to-end anastomosis. The malrotation of the intestine was not completely corrected.

Postoperatively, the child did surprisingly well. The bowel movements were normal following the fourth postoperative day. A gradual increase in weight and health was noted and upon the seventeenth day postoperatively the child was dismissed from the hospital. This child is living and well two and one-half years later.

CASE 3.—Baby girl, No. 58204, aged 3 months. This child had a diarrhea for two days prior to being seen at the Clinic. At the time of the first examination, the typical bloody, mucouslike stool was present in the diaper. Vomiting had been noted for three days. The child was dehydrated and toxic. A mass was felt in the abdomen on the right side which was of a sausage-like character. The rectal examination was essentially negative, except for blood on the examining finger. A diagnosis of intussusception was made.

Following subcutaneous fluids under the direction of the pediatrician, the child was operated upon. The lower portion of the small bowel had intussuscepted into almost the entire right side of the colon. Reduction was done in the usual manner by taxis as gently as possible in approximately twenty minutes. At the end of that time, it was obvious that the reduced intestine would never live. Approximately 4 inches of the terminal ileum were gangrenous and necrotic. A resection of 15 cm. of terminal ileum was done utilizing end-to-end anastomosis. On the second postoperative day, the child had a bloody bowel movement, followed by a healthy increase in appetite and an uneventful recovery. This child is living and well two years postoperatively.

DISCUSSION

In recent years more reports have been appearing in the literature referable to intestinal resection as a primary procedure. As suggested by Benson and Sharpe[1] the reduced mortality rate is due to:

1. The use of a few hours preoperatively to correct fluid imbalance.
2. The use of blood.
3. Better anesthesia.
4. Chemotherapeutic agents.

Ladd and Gross,[9] in their series of forty-three patients, noted a 75 per cent mortality rate in those children operated upon for gangrenous intussusception. Eighteen of these resections were combined with anastomoses of the intestines, and twenty-five had a Mikuliez type of procedure. A large number of these operations were done prior to the advent of the more recent chemotherapeutic drugs. In 1945, Hindmarsh and associates[7] reported two infants who survived a Mikuliez type of procedure. Tedesco[12] has reported the successful survival of one

infant 6 months old following resection with open end-to-end anastomosis between the ileum and transverse colon. Hesser and co-workers[6] in 1952 have stated that resection with primary anastomosis should be advocated in all cases of irreducible gangrenous intussusception. However, they make it quite clear that a short circuit to relieve the obstruction may be good judgment in the poor risk patient.

Certainly when one is confronted with gangrenous intestine the best and most logical procedure would be primary intestinal resection and anastomosis. However, the poor risk infant below the age of one year may well not stand such a procedure. If, in the judgment of the surgeon, such a primary resection is not feasible, a lateral anastomosis or a Mikulicz type of procedure may be useful.

CONCLUSION

1. Primary intestinal resection in infants is not the formidable procedure it was considered in the past.

2. In certain select cases primary intestinal resection could well be the procedure of choice.

3. In the future, with the aid of the new antibiotics and better preoperative preparation, we shall probably be able to avoid the Mikulicz type of procedure in infants.

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SEPTIC ARTHRITIS AND OSTEOMYELITIS IN INFANCY

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OSTEOMYELITIS in the newborn and in the young infant has been recorded by various authors. Fraser[1] in four years collected thirty cases following umbilical sepsis. Mount[2] reported a fatal case affecting the humerus. Green and Shannon[3] recorded a mortality rate of 45 per cent in a series of twenty-three cases occurring in the first six months of life. Einstein and Thomas[4] noted the frequent joint involvement in this disease. Thomson and Lewis[5] reported four cases in immature infants. Hutter[6] illustrated the effectiveness of sulfonamides and penicillin therapy in reducing mortality in hemolytic staphylococcal osteomyelitis in the first six months of life. He recorded a mortality rate of 58 per cent in the period 1934 to 1943 (twelve cases) compared with no deaths in six cases treated with chemotherapy and penicillin between 1943 and 1947. Blanche[7] stressed the fact that absence of pyrexia and general reaction to infection may be misleading in these cases. He emphasized the rapid course of the disease, and that late diagnosis may lead to irreparable joint damage. We wish to record six cases, three of which occurred in the neonatal period, and the other three in infancy. The importance of early treatment with regard to ultimate functional and anatomical recovery is illustrated by the late clinical and radiological studies undertaken some years after the initial acute illness.

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CASE REPORTS

CASE 1.—N. P., a boy aged 20 days, was hospitalized for thirty-one days. The pregnancy and labor were normal. Four days before admission he suddenly developed a swelling of the left knee. This was followed three days later by a swelling of the left elbow and right wrist. There was no history of trauma, fever, or infection. On examination the infant was apyrexial. The umbilicus was dirty, but there was no pus. The left knee was swollen, red and hot, with superficial dilated veins and an effusion into the joint. The whole left thigh was swollen and hot. The left elbow region and the right wrist showed similar signs. All movements at these joints were restricted.

Hemolytic streptococci were cultured from pus aspirated from the left knee joint. The blood Wassermann reaction, gonococcal fixation test, and blood cultures were negative. Blood count was as follows: hemoglobin 18.9 Gm. per cent, red blood corpuscles 4,780,000 per cubic millimeter, leukocytes 18,500 per cubic millimeter, neutrophils 73.5 per cent, monocytes 2 per cent, lymphocytes 24.5 per cent.

Radiographs taken on the eighth day after the onset in the left knee, that is, on the fifth day after involvement of the left elbow and the right wrist, showed marked soft tissue swelling about these joints with more

or less obliteration of the skin folds (Fig. 1). These folds, which are due to absence of subcutaneous fat and loose skin, were visible about the corresponding normal joints (Fig. 1, *A* and *B*). The only direct evidence of bone involvement was slight localized osteoporosis and blurring of the trabeculae in the lower end of the left humerus. Ten days later there was a florid periosteal reaction on the posterior and medial aspects of the lower end of the left femur, with slight blurring of the trabeculae and localized osteoporosis here. The swelling was less. The left elbow at this stage showed similar changes with periosteal reaction on the humerus and the ulna, and with areas of destruction in the ulna (Fig. 2). The wrist showed no change in either the soft tissue swelling or the normal-looking bones. Films taken eight days later showed no change, and thereafter there was a gradual return to normal, so that on the sixty-seventh day there was nothing more than a slight coarsening of the trabecular structure. Three years later the bones were normal.

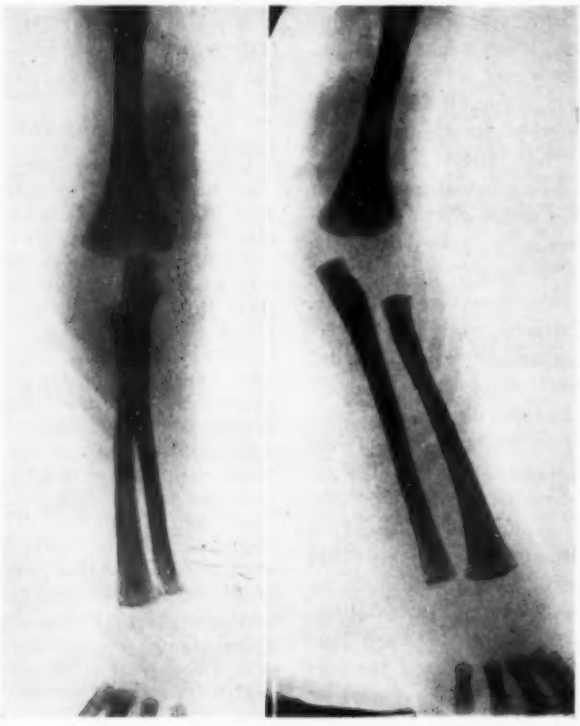

Fig. 1 (Case 1).—Showing the skin folds about the unaffected right elbow and left wrist, and the obliteration of these folds by the soft tissue swelling about the affected left elbow and right wrist.

Treatment consisted of penicillin 50,000 units intramuscularly every three hours for four weeks, with one aspiration of each affected joint, and local instillation of penicillin.

CASE 2.—J. C., a boy aged 6 weeks, was in hospital for twenty-five days. The pregnancy and labor were normal. Two days before admission he sud-

denly developed a hot, red, painful, and swollen left knee. There was no fever, and the infant was eating and sleeping normally. On examination he was apyrexial and normal except for the left knee, which was one-half inch greater in circumference than the right. The movements were limited and the swelling felt like a bony enlargement of the lower end of the femur with no joint involvement. The hip joint was normal. The swelling increased in the first four days of hospitalization.

Aspiration of the joint yielded sterile pus. Blood count was: hemoglobin

Fig. 2 (Case 1).—Showing periosteal reaction on the humerus and ulna with areas of destruction in the ulna.

9.4 Gm. per cent, red blood corpuscles 2,940,000 per cubic millimeter, leukocytes 10,100 per cubic millimeter, neutrophils 56.5 per cent, monocytes 8 per cent, lymphocytes 32.5 per cent, eosinophils 2 per cent, basophils 1 per cent. The Mantoux and gonococcal complement fixation tests and the blood Wassermann reaction were negative.

Radiographs taken twenty-four hours after the onset showed slight soft tissue swelling about the knee and thigh, with irregularity and loss of definition of the musculosubcutaneous plane. One week later the swelling was unchanged but the tissue planes were well defined, and there was a periosteal reaction on the anterior aspect of the lower end of the femur. Between the eighth and the thirty-ninth day the soft tissue swelling and the periosteal reaction subsided, and on the one hundred fifteenth day there was no evidence of pathology.

He was given penicillin intramuscularly for two weeks.

Case 3.—L. B., a girl aged 3 months, was hospitalized for thirty-six days. The pregnancy and labor were normal. Three weeks before admission she developed bronchitis and after a week the left leg became swollen and painful. On examination the temperature was 100° F. and the left knee was swollen, red, hot, and tender, with prominent veins over it. There was an effusion into the joint with limitation of movement.

Aspiration produced sterile pus. The Wassermann reaction, Paul Bunnell test, blood cultures and typhoid-paratyphoid and brucellosis agglutination tests were all negative.

Radiographs taken on the fourteenth day of the illness showed soft tissue swelling and loss of definition and irregularity of the fascial planes about the knee joint, with no direct evidence of bone involvement. On the thirty-first day the soft tissue swelling was much less, and there was a well-marked periosteal reaction on the medial and lateral aspects of the lower end of the femur. On the fifty-third day the linear periosteal reaction was barely detectable. Three years later the epiphyses of the affected joint were slightly larger than those on the opposite side (Fig. 3). The length of the bones was normal.

The infant was given penicillin intramuscularly for five weeks.

CASE 4.—S. B., a boy aged 28 days, was hospitalized for thirty-three days. The pregnancy was normal, with a breech delivery. The infant was well until two weeks before admission when the mother noticed that he would not move his left arm. There was no history of trauma or infection. On examination the temperature was 100° F. The left shoulder was swollen and the arm was held in the "porter's tip" position. There was gross limitation of movement. The left axilla was swollen due to enlarged glands and soft tissue swelling.

The Wassermann reaction was negative. Blood count was: hemoglobin 9.4 Gm. per cent, red blood corpuscles 4,250,000 per cubic millimeter, leuko-

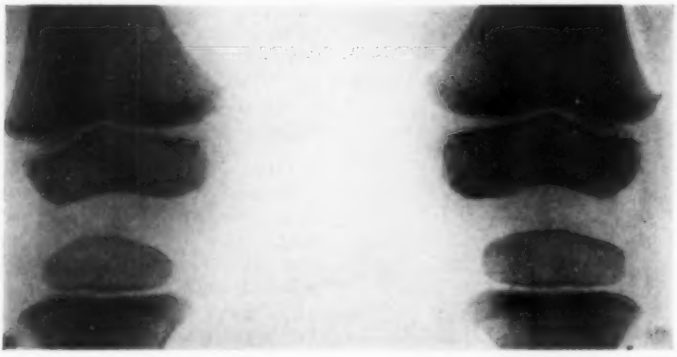

Fig. 3 (Case 3).—Showing the slightly larger epiphyses on the affected left side.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4 (Case 4).—Showing the area of erosion with an ill-defined margin in the metaphysis, and the subluxation. Note the absence of periosteal reaction.

Fig. 5 (Case 4).—Showing definition of the erosion (compare with Fig. 4), and less subluxation.

Fig. 6 (Case 4).—Showing the final slight deformity: shallow and irregular glenoid, broad and irregular epiphyses and neck, and coarsened trabeculation.

cytes 25,000 per cubic millimeter, neutrophils 34 per cent, monocytes 3 per cent, lymphocytes 60 per cent, eosinophils 3 per cent.

Radiographs taken on the ninth day of the illness showed soft tissue swelling with good definition of the musculosubcutaneous plane. There was an area of erosion with an ill-defined margin in the metaphysis of the head of the humerus which was subluxed (Fig. 4). There was no periosteal reaction. On the thirteenth day the swelling was less, the erosion had well-defined margins, and the subluxation had increased. On the twenty-seventh day the swelling had subsided, the subluxation was minimal, and the erosion was well defined (Fig. 5). By the thirty-seventh day there was slight sclerosis about the area of erosion, and trabeculae were visible within it. There was no soft tissue swelling or subluxation. Three years later the epiphyses were more irregular in outline and in calcification, and smaller in size than those of the opposite side, the neck was broader with coarser trabeculation, and the glenoid was shallow and irregular (Fig. 6).

He was treated with penicillin intramuscularly for twenty-eight days.

CASE 5.—O. R., a boy aged 8 months, was hospitalized for twenty-nine days. The pregnancy and labor were normal. He was well until four days before admission when he developed a pyrexia which persisted until admission, when the right wrist and right knee became swollen. On examination he weighed 19 pounds. The temperature was 101.8° F. There was swelling of the dorsum of the right hand which was tender, and the right knee was swollen and tender and one-half inch greater in diameter than the left.

The Wassermann reaction and the typhoid-paratyphoid and brucella agglutination tests were negative. Blood count was: hemoglobin 9.9 Gm. per cent, red blood corpuscles 3,400,000 per cubic millimeter, leukocytes 45,000 per cubic millimeter, neutrophils 43 per cent, monocytes 5 per cent, lymphocytes 50 per cent, eosinophils 2 per cent.

Radiographs taken on the sixth day of the illness showed only slight soft tissue swelling. Loss of definition of the musculosubcutaneous planes and edema of the subcutaneous fat was confined to the sites of intramuscular injections, and was not considered to be pathological. On the thirteenth day there was an effusion into the joint, but there was no direct evidence of bone involvement. On the twenty-fourth day there was no evidence of pathology.

Penicillin by intramuscular injection was given for four weeks.

CASE 6.—L. H., a girl aged 17 days, was hospitalized for forty days. The pregnancy and labor were normal. The infant was well until eight days before admission when she developed swelling of the right elbow. Four days before admission the middle finger of the left hand became swollen. On examination the temperature was 101° F. There was a hot, red, tender, fluctuant swelling of the right elbow, but movement at the joint was not painful. The axillary lymph glands were enlarged. There was a similar hot, red, tender swelling of the middle finger of the left hand, with extreme pain on movement.

Pus from the elbow joint yielded a pure growth of *Staphylococcus aureus* sensitive to penicillin and streptomycin. Blood culture and blood Wassermann reaction were negative. Blood count was: hemoglobin 15 Gm. per cent, red blood corpuscles 4,750,000 per cubic millimeter, leukocytes 23,000 per cubic millimeter, neutrophils 37 per cent, monocytes 6 per cent, lymphocytes 55.5 per cent, eosinophils 1.5 per cent.

Radiographs taken on the twelfth day after the onset of the disease in the right elbow, that is on the eighth day of involvement of the left middle finger, showed marked soft tissue swelling at both these sites, but no

other evidence of abnormality in the finger. In the elbow there was loss of definition and irregularity of the musculosubcutaneous plane. There were areas of erosion and of sequestration in the upper two-thirds of the ulna, and there was a well-marked periosteal reaction on both the ulna and the humerus (Fig. 7). On the seventeenth day the swelling had disappeared. There was a definite involucrum, without cloacae, and with several separated sequestrae. On the twenty-seventh day there was no change. Three years later there was slight deformity of the olecranon, with a relatively shallow coronoid notch. The trabeculae were irregular and the upper end of the ulna was slightly widened. The olecranon fossa of the humerus was shallow and elongated vertically.

Fig. 7 (Case 6).—Showing areas of erosion in the ulna, with sequestration and with periosteal reaction on both ulna and humerus.

Penicillin was given by injection for thirty-five days.

DISCUSSION

Of these six cases, four boys and two girls, three were confined to the neonatal period, with ages varying from 17 to 28 days, and three were under 8 months of age. Four presented with a painful, red swelling of the affected part in an otherwise apparently well child. One had a pyrexia of four days' duration before the appearance of the swelling, and one presented with a pseudoparalysis of the affected limb. In this case, the swelling only became apparent some days later. The lesion was always situated in the vicinity of a joint, or in the joint itself. Three infants had a single lesion, two had double lesions, and one had three affected areas. The left knee was involved in three cases, the right wrist in two, and the right elbow, right knee, left elbow, left middle finger, and left shoulder in one case each. We could find no portal of entry for the infection and there was only minimal constitutional disturbance in all, though four infants had fever. The parts affected were extremely tender in every case. Anemia was present in four cases and well-marked leukocytosis was also present in four patients, the highest leukocyte count reaching a level of 45,000 per cubic millimeter. Pus was aspirated in four cases, and cultivation yielded a hemolytic streptococcus in one, and a *Staph. aureus* in another. No organisms were found in the other cases aspirated. Intramuscular penicillin therapy was instituted in all with the addition of local instillation of penicillin in two cases.

TABLE I

CASE	AGE	SEX	PERIOD HOSPITALIZED	MAIN SYMPTOM	PYREXIA	HEMOGLOBIN (GM. %)	ERYTHROCYTES (MILLIONS PER C.MM.)	LEUKOCYTES (PER C.MM.)	PART AFFECTED	ASPIRATION	FOLLOW-UP
1. N. P.	20 da.	M	31 da.	Painful swelling	No	18.9	4.78	18,500	L. knee L. elbow R. wrist	Pus cells Hemolytic streptococcus	Yes
2. J. C.	6 wk.	M	25 da.	Painful red, swelling	No	9.4	2.94	10,100	L. knee	Pus cells	No
3. L. B.	3 mo.	F	36 da.	Painful red, hot swelling	Yes	8.9	3.13	11,400	L. knee	Pus cells	Yes
4. S. B.	28 da.	M	33 da.	Pseudoparalysis	Yes	9.4	4.25	25,100	L. shoulder		Yes
5. O. R.	8 mo.	M	29 da.	Painful red, hot swelling	Yes	9.9	3.4	45,000	R. wrist R. knee		No
6. L. H.	17 da.	F	40 da.	Painful red, hot swelling	Yes	15	4.75	23,000	R. elbow L. middle finger	Pus cells *Staph. aureus*	Yes

TABLE II

CASE	SITE	AGE	DAY OF DISEASE	SOFT TISSUE SWELLING	MUSCULO SUBCUTANEOUS EDEMA	BONE CHANGES FIRST X-RAY	PERIOSTEAL REACTION	DESTRUCTION	JOINT INVOLVEMENT	RESIDUAL BONE CHANGES
1. N. P.	L. knee	20 da.	8	+	0	None	18th day	18th day	Effusion	None
	L. elbow		5	+	0	None	15th day	15th day	Effusion	None
	R. wrist		5	+	0	None	None	None	Effusion	None
2. J. C.	L. knee	6 wk.	1	+	+	None	8th day	None	Effusion	—
3. L. B.	L. knee	3 mo.	14	+	+	None	31st day	None	Effusion	Increased size of epiphyses
4. S. B.	L. shoulder	28 da.	9	+	0	Destruction	None	Increased destruction	Dislocation	Small, irregular epiphysis
5. O. R.	R. wrist	8 mo.	6		0	0	0	0	Effusion	—
	R. knee		6	+	0	0	26th day	0	Effusion	
6. L. H.	R. elbow	17 da.	12	+	0	Destruction + periosteal reaction	12th day	12th day	Effusion	Deformity large epiphyses
	L. finger		8	+	0	0	0	0	None	—

There were no fatalities and no chronic sinuses developed. Hospitalization varied from twenty-five to forty days. Four cases were followed up for a period of three years. One patient showed some limitation of extension at the right elbow joint and the others were normal.

The radiological features are summarized in Table II.

Soft tissue swelling was present in every case at the time of the first radiological examination, but edema of the musculosubcutaneous plane was present only in Cases 2 and 3. Only two cases (4 and 6) showed destruction of bone and at three of the sites of infection there was no direct evidence of bone involvement. In every case the joints were involved, in some without evidence of bone involvement.

The follow-up studies are not unusual Two patients showed enlargement of epiphyses, due to hyperemia, while two showed a slight aberration of growth, manifest by coarsening and irregularity of the trabecular structure and deformity of the bones. The infection is said to be blood-borne and the multiplicity of lesions in several cases supports this. The absence of trauma or of any obvious source of infection favors the view that the illness started as a mild bacteremia. The mildness of the bacteremia is illustrated by the minimal consitutional effects found in this series. The prognosis with early treatment is good, but in untreated patients it is extremely bad with a high mortality or late severe deformity (I. K., to be published).

SUMMARY

Six cases of septic osteomyelitis and arthritis in infancy are reported. Four of these occurred in the neonatal period, and the other two were under 8 months of age. Four males and two females were affected. In four of this series, the patients were followed up for three years, and these showed excellent functional recovery. All these patients were submitted to intensive penicillin therapy as soon as possible.

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A METHOD FOR THE MEASUREMENT OF CEREBRAL BLOOD FLOW IN INFANTS AND CHILDREN

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THE most practical means for the measurement of cerebral blood flow in human beings is the nitrous oxide method. This method involves the inhalation of a nitrous oxide mixture for a period of ten minutes and the measurement of the rise in inert gas in arterial and cerebral venous blood samples taken during this period. Kety,[1, 2] Scheinberg,[3] and others have shown this method to be satisfactory for adults. It is not applicable for use for infants and small children because the laboratory determinations require 70 to 100 c.c. of blood. Technical difficulties also arise from the small size of the blood vessels and from the inability of the patient to cooperate. However, the principles outlined by Kety are applicable in young children if the method for gas analysis utilizes small amounts of blood.

METHOD

Samples of blood are withdrawn from the arterial and the cerebral venous circulations at timed intervals after the patient begins breathing a nitrous oxide-oxygen mixture. The levels of nitrous oxide measured in these samples are plotted against the time of their withdrawal, and the points on the graph are connected to form arterial and venous curves of nitrous oxide content. The area between the arterial and venous curves is a function of the cerebral blood flow during the time of sampling. As shown by Kety, this relation may be expressed by the equation:

$$CBF = \frac{100\ V_t S}{\int_o^t (A\text{-}V)dt} = \text{c.c./100 Gm./min.}$$

where V_t is the nitrous oxide content of cerebral venous blood when in equilibrium with brain tissue,
S is the distribution ratio of nitrous oxide between blood and brain, and
$\int_o^t (A\text{-}V)dt$ is the integral of the arteriovenous difference of nitrous oxide in volume per cent from onset of inhalation (o) to equilibrium time (t), which is ten minutes.

EQUIPMENT REQUIRED

1. Douglas bag with tubing and one-way valve. The bag is filled with a mixture of 20 per cent nitrous oxide and 80 per cent oxygen, sufficient for a ten-minute period of gas inhalation.

2. Twelve 5 c.c. heparinized syringes. These are prepared by evaporating 2 c.c. of a solution of heparin (20 mg. per 100 c.c.) from the barrels. A thin coat of light mineral oil is applied to each plunger. A snugly fitted cap seals each syringe.

3. No. 20 Murphy-Gardner type needle. This can be made by connecting a No. 20 hubless needle and a blunt

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This study was made possible in part by a grant from the Pennsylvania Society for Crippled Children and Adults, Inc.

This paper was presented in part before the meetings of the Society for Pediatric Research at Old Point Comfort, Va., May 5, 6, 7, 1952.

No. 15 needle by a 10 cm. length of polyethylene tubing.

4. Two 10 c.c. syringes. Each syringe contains 5 mg. of heparin in 3 c.c. of physiologic saline solution.

PREPARATION OF THE PATIENT

The patients are fasted and sedated as for a general anesthetic. Premedication consists of Seconal and atropine, given according to age and weight one hour before the procedure. The patient is placed in the supine position. The arms are restrained to the sides, and the legs are fastened in the frog-leg position. Pentothal is given intravenously, if additional sedation is required. The head is rotated to the left, and a No. 20 needle is inserted into the internal jugular bulb.* Connection of the needle to a three-way stopcock and through it to an infusion of physiologic saline solution completes the unit for intravenous administration. A No. 20 Murphy-Gardner type needle is then inserted into a femoral artery after infiltration of the area with 1 per cent procaine. A three-way stopcock connects the needle to one of the 10 c.c. syringes containing heparin solution.

While these procedures are in progress, and for a total of twenty to thirty minutes, the patient inhales 100 per cent oxygen to wash excess nitrogen from the blood, after which initial arterial and venous samples are drawn. The patient then breathes a mixture of 20 per cent nitrous oxide and 80 per cent oxygen for a period of ten minutes. Five serial arterial and venous samples of 1 c.c. each are drawn at accurately timed intervals during the ten-minute period of gas inhalation and placed immediately in ice. Specimens are taken more frequently during the first four minutes, when the blood content of nitrous oxide is changing rapidly. Before a sample is taken, each system is cleared by wasting 1 c.c. of blood into a syringe containing heparin solution. Clotting in the arterial system is prevented by closure of the stopcock while 1 c.c. of the blood-heparin mixture is pushed in. At the conclusion of the procedure the remainder of the waste heparinized blood is returned to the patient.

Gas analyses are performed by the syringe analyzer method of Scholander.[5] Each sample is delivered from the specially prepared sealed syringe into a 40 microliter pipette.* Transfer of the blood into the syringe analyzer and the determination of nitrous oxide are performed according to the method of Edwards, Scholander, and Roughton.[6, 7]

RESULTS

Satisfactory cerebral blood flow studies have been made on twenty-seven infants and small children whose ages range from 4 weeks to 7 years. Nine of them were less than 2 years of age. Normal children have not been studied. The clinical diagnoses of the patients studied include hydrocephalus (twelve cases), spastic quadriplegia (six cases), mental retardation (five cases), hemihypertrophy (one case), hypothyroidism (one case), carotid-

*The external landmarks for this procedure are the tip of the mastoid and the posterior wall of the external auditory canal. The needle is inserted 1 cm. below and 1 cm. in front of the tip of the mastoid. The direction of the needle is toward the posterior wall of the external auditory canal at an angle of 45 to 60 degrees. If bony obstruction is met, the angle of the needle is increased or decreased in the same plane. In small infants the direction of the needle is more nearly perpendicular to the neck.[4]

*The syringe analyzer and pipette may be obtained from J. D. Graham, School of Medicine, University of Pennsylvania.

jugular anastomosis (one case), and cerebellar ataxia (one case).

In Fig. 1 are shown the data depicting the cerebral blood flow of a four-year-old child whose clinical diagnosis was mental retardation. Table I shows the method of calculation of these data. Table II and Fig. 2 demonstrate simi-

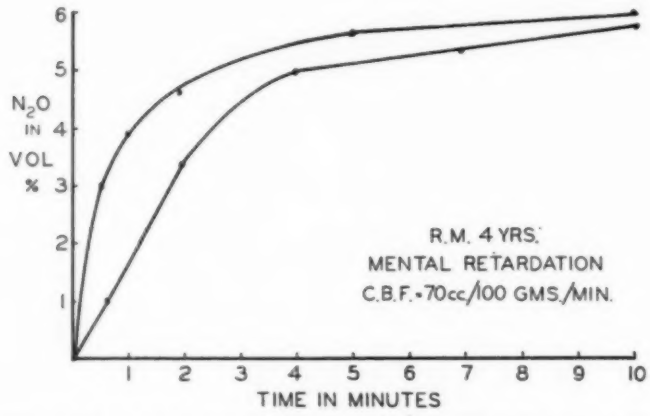

Fig. 1.—Cerebral blood flow in a child with mental retardation. The nitrous oxide content in volumes per cent of each arterial and venous sample is plotted against the time of the inhalation of the gas. The area between the arterial (upper) and venous (lower) curves is a function of cerebral blood flow (C.B.F.), which can be expressed in cubic centimeters of blood per 100 grams of brain per minute. These curves show that the arterial nitrous oxide content rises quickly and levels off. The venous curve rises more slowly and approaches the arterial level at ten minutes.

TABLE I. DATA FOR FIG. 1

t MIN.	ART. N_2O VOL. %	VENOUS N_2O VOL. %	$(A\text{-}V)_{N_2O}$	$\int_{t-1}^{t}(A\text{-}V)dt$	$\int_{0}^{t}(A\text{-}V)dt$
1	–	–	–	1.30	1.30
2	4.40	2.50	1.90	2.30	3.60
3	5.00	4.00	1.00	1.45	5.05
4	5.35	4.78	0.57	0.79	5.84
5	5.54	5.10	0.44	0.50	6.34
6	5.65	5.20	0.45	0.45	6.79
7	5.70	5.30	0.40	0.42	7.21
8	5.80	5.40	0.40	0.40	7.61
9	5.85	5.55	0.30	0.35	7.96
10	5.90	5.70	0.20	0.25	8.21

$$CBF = \frac{V_t = 5.76}{\dfrac{100\ V_t S}{\int_0^t (A\text{-}V)dt}} = \frac{5.76 \times 100}{8.21} = 70 \text{ c.c./100 Gm./min.}$$

$(A\text{-}V)\ N_2O$ = Cerebral arteriovenous nitrous oxide difference.

$\int_{t-1}^{t}(A\text{-}V)dt$ = Area between arterial and venous curves in one minute.

$\int_{0}^{t}(A\text{-}V)dt$ = Summed areas between the curves.

Vt = Cerebral venous nitrous content at time t, which is 10 minutes.
S = 1.0, the distribution ratio of nitrous oxide between blood and brain.

lar data from a hydrocephalic patient with marked mental and physical retardation.

Of the twelve patients with hydrocephalus, nine were markedly retarded mentally and physically. All of these had reduced cerebral blood flows by comparison with adult standards. One 10-month-old infant and two 6-year-old children, each of whose mental and physical development was considered average for age, had normal curves.

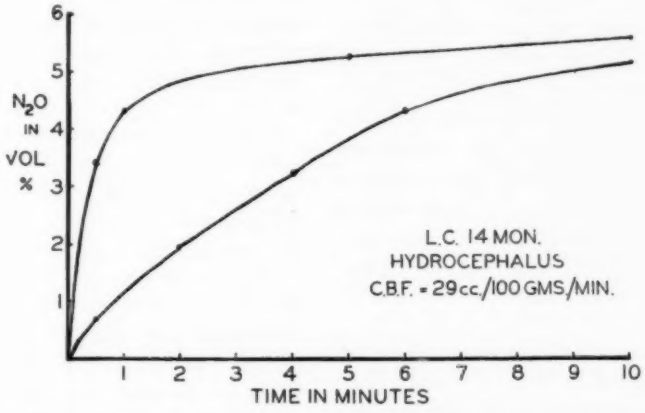

Fig. 2.—Cerebral blood flow in an infant with hydrocephalus. A comparison of this curve with Fig. 1 shows that the arterial nitrous oxide content again rises quickly. However, the venous curve rises slowly so that the area between the two curves is markedly increased.

TABLE II. DATA FOR FIG. 2

t MIN.	ART. N_2O VOL. %	VENOUS N_2O VOL. %	$(A\text{-}V)N_2O$	$\int_{t-1}^{t}(A\text{-}V)dt$	$\int_{0}^{t}(A\text{-}V)dt$
1	—	—	—	2.90	2.90
2	4.60	1.60	3.00	3.05	5.95
3	4.90	2.30	2.60	2.80	8.75
4	5.10	2.90	2.20	2.40	11.15
5	5.20	3.50	1.70	2.05	13.20
6	5.30	4.10	1.20	1.45	14.65
7	5.35	4.50	.85	1.02	15.67
8	5.40	4.70	.70	.75	16.40
9	5.45	4.90	.55	.62	17.02
10	5.50	5.10	.40	.45	17.45

$$CBF = \frac{100\ V_t S}{\int_0^t (A\text{-}V)dt} = \frac{5.2 \times 100}{17.45} = 29 \text{ c.c./100 Gm./min.}$$

$V_t = 5.2$

(A-V) N_2O = Cerebral arteriovenous nitrous oxide difference.

$\int_{t-1}^{t}(A\text{-}V)dt$ = Area between arterial and venous curves in one minute.

$\int_{0}^{t}(A\text{-}V)dt$ = Summed areas between the curves.

Vt = Cerebral venous nitrous content at time t, which is 10 minutes.
S = 1.0, the distribution ratio of nitrous oxide between blood and brain.

One infant has been studied before and after a lumbar subarachnoid-peritoneal shunt procedure. No significant increase in cerebral blood flow was demonstrable one week postoperatively.

DISCUSSION

The nitrous oxide method, as described by Kety, is based upon three assumptions: (1) that nitrous oxide in the low concentrations used is physiologically inert; (2) that equilibrium of gas in the blood and brain is reached within ten minutes, with the solubility ratio between them being equal to one; (3) that blood from either internal jugular bulb represents mixed cerebral venous blood.

Sedation must be employed to obtain a smooth inhalation curve. Barbiturate anesthesia is known to have a depressant effect on cerebral circulation and cerebral oxygen consumption,[8, 9, 10] but there appears to be no way of avoiding this difficulty in the young, uncooperative patient. Analgesic rather than anesthetic doses are used.

In the opinion of some investigators,[11] the administration of O_2 before the inhalation of nitrous oxide tends to decrease the cerebral blood flow by as much as 13 per cent.* Page and associates[12] found no significant effect on the cerebral blood flow, although there was a decrease in cerebral oxygen consumption. The N_2O-O_2 mixture has been used because of its ready availability and low cost. The use of a Douglas bag insures a constant gas mixture.

*The preliminary period of O_2 inhalation is unnecessary if a commercially prepared mixture of nitrogen (65 per cent), oxygen (20 per cent), and nitrous oxide (15 per cent) is used.

It seems generally agreed that, in the great majority of individuals, blood from either internal jugular vein at the level of the superior bulb is fairly representative of mixed cerebral venous blood.[13] This opinion is substantiated by the data from two of our patients from whom samples of blood were drawn simultaneously from each side. The amount of contamination by blood from extracerebral sources at the level of the internal jugular bulb is considered insignificant.

The details of the Scholander method are available elsewhere.[5, 6, 7] In our experience the principal difficulty has been in avoiding the resorption of gas. The gas should be placed in the capillary tube immediately following completion of the reaction. Once the gas has been placed in the capillary tube, it should not be brought down again into the chamber. A mistake made in any part of the procedure is usually readily apparent. Forty to forty-five analyses can be performed in an eight-hour day by a competent technician. Breakage is minimal with the syringe analyzers that are now available. A 1 c.c. specimen of blood is adequate for the determination of nitrous oxide and of oxygen in triplicate.

Results are reproducible within one-tenth of a division on the syringe analyzer. Scholander has shown that the methods of analysis employed by his group are quite accurate when compared to the method of Peters and Van Slyke, which requires a much larger volume of blood.[6, 7]

A different method of calculation of cerebral blood flow has been described by Scheinberg and Stead.[3] This method necessitates the taking of only

three pairs of arterial and venous samples: initial, integrated, and final. During the ten-minute period of gas inhalation, arterial and venous blood specimens are withdrawn at constant rates. This technique requires over 50 c.c. of blood but only half the number of of gas analyses. However, in our opinion the plotting of a curve would seem to provide an additional and desirable check of the data.

CONCLUSIONS

(1) An adaptation of the Kety nitrous oxide method for the determination of cerebral blood flow has been described. It is practical and safe for use in infants and children.

(2) Preliminary observations suggest, but do not establish, that there may be significant changes in cerebral blood flow in hydrocephalic patients who are mentally and physically retarded.

(3) Further studies are in progress to determine cerebral blood flow in a variety of neurological conditions and, when possible, before and after neurosurgical procedures.

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THE TREATMENT OF PINWORM INFECTION (ENTEROBIASIS) WITH PAPAIN

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IN THE past decade investigators from all parts of the world have reported on the high incidence, methods of diagnosis, and the treatment of pinworm infection.[1] Many drugs have been used by mouth, in enemas, and as topical applications.[2] In addition to drug therapy, various mechanical as well as personal and environmental hygienic measures have been recommended to control pinworm infection. Among the most widely used oxyuricides are gentian violet, phenothiazine, Diphenan, hexylresorcinol, orally and in enemas, and tetrachloroethylene. Among the newer oxyuricides are terramycin, Egressin, garlic (raw and as deodorized tablets) and papain, a vegetable enzyme. The authors treated four series of forty patients each with four of these oxyuricides. Egressin was effective in 52 per cent, diphenan in 30 per cent, gentian violet in 82 per cent, and terramycin in 84 per cent of the patients treated. However, even those oxyuricides that have the higest cure rates are not entirely satisfactory. Gentian violet in some cases causes abdominal cramps with nausea and vomiting, and the younger children, most usually, are unable to swallow the intact tablets. Terramycin, while effective in a high percentage of cases, is an expensive medication, particularly when an entire family is treated with this drug. Oxyuricides which have been used less extensively are bacitracin, Lubisan, Aeranil, Atabrine, Benadryl, Peperazine, Pyribenzamine, santonin, and Quassia chips. Because of questionable efficieney or toxicity, many of these drugs have been discarded as oxyuricides.

Weise[3] treated a series of sixty patients infected with *Enterobius vermicularis* with papain plus the usual precautions of strict personal hygiene. He reported "uniform success" in all patients treated and in none of the patients could oxyurids be observed following treatment. All of these patients remained worm-free for at least six weeks following treatment with papain.

Sollman[4] describes papain as the dried milk juice of the unripe fruit of the "melon tree," *Carica papaya*. Papain, a vegetable enzyme, is more variable and less active than pepsin and converts proteins to amino acids, in acid, neutral or alkaline media (pH 4-7). Its chief use is in the tenderization of meats. The potency[5] of commercial papain varies according to the process of preparation. The usual grade digests about thirty-five times its weight in lean meat, while the best grades render soluble 200 to 300 times their weight of coagulated egg albumin in alkaline media. Papain[6] has been crystallized and its chief medical

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use has been to prevent adhesion in sloughing and infected wounds. Commercially it is also known as Caroid, papayotin, and papoid.[7]

Weise[3] demonstrated that in in vitro trials the digestive action of papain is manifested primarily by the perforation of the cuticle and erosion of the body wall of the *E. vermicularis*, and secondarily by the gradual maceration and digestion of the viscera of the worm. Weise has also pointed out that this process is more intense and quicker in vivo because of the added action of the intestinal enzymes trypsin and erepsin which enter the body of the worm after its cuticle has been eroded.

DOSAGE OF PAPAIN

On the evening preceding treatment with papain, a magnesium sulfate laxative was administered to the patients so that at the time of treatment with papain the intestinal tract was empty and no protein other than the worm substance was present in the intestinal tract. On the next morning following a light, protein-free breakfast, the children were given three sugar-coated tablets of 250 mg. each at hourly intervals for four hours, a total of 12 tablets or 3 Gm. of papain. The adults were given four tablets of 250 mg. each at hourly intervals for four doses, a total of 16 tablets or 4 Gm. of papain. No food was taken until two hours after the last dose of papain was taken. Those patients who could not swallow the tablets were given a 5 per cent alcohol solution of papain containing 0.5 Gm. of papain to the teaspoon. The total dose of liquid papain was the same as the total dose in the tablet form. In addition to the papain treatment the usually recommended personal and environmental hygienic measures were adhered to as closely as possible.

TABLE I

NO. OF PATIENTS	POSITIVE POST-TREATMENT SMEARS	
	NO.	%
11	7	100
3	6	86
1	5	71
5	4	57
5	3	43
1	2	29
2	1	14

CLINICAL MATERIAL AND METHOD

Thirty patients infected with *E. vermicularis* were treated with papain at the Edward J. Meyer Memorial Hospital in Buffalo, N. Y. The patients treated ranged in age from 20 months to 32 years. The diagnosis was established by the use of a modification of the Graham Scotch tape swab technique which we have described in detail in an earlier publication.[8] Seven days after treatment, Scotch tape swab smears were made daily for one week to determine the results of the treatment. Those patients who had seven consecutive negative smears were declared cured.

RESULTS OF TREATMENT

Of the thirty patients treated by this method only two patients had seven consecutive post-treatment nega-

tive Scotch tape smears. The remaining twenty-eight patients had one to seven positive post-treatment smears. The cure rate in this series of patients treated with papain was only 7 per cent. However, one of the two patients considered cured had a positive smear on the eighth day and therefore must be considered a failure. Two of the twenty-nine unsuccessfully treated patients had only one positive smear on the first post-treatment period and six negative smears on the following six consecutive days. If these two patients are included in the group of successfully treated patients, and the one with a positive smear on the eighth day is excluded, the corrected cure rate would be 10 per cent.

Table I compares the number of patients with the number of positive post-treatment smears. All these smears were taken seven days following treatment. A correlation of the number of positive smears with the number of patients unsuccessfully treated illustrates the degree of failure of treatment.

DISCUSSION

In this series of cases treated with the vegetable enzyme, papain, we have not been able to confirm the exceptionally good results reported by Weise. We used the same dose of papain as used by Weise, a total of 3 Gm. for one day in treating the children and 4 Gm. for one day in treating the adults. In addition to the drug therapy all these patients followed the usually recommended personal and environmental hygienic measures. While Weise determined his cure rate by the presence or absence of worms in the stools, we determined our cures by the examination of Scotch tape smears for eggs. Sufficient data can be found in the literature proving the superiority of the Scotch tape smear technique over the stool examination technique in the diagnosis of enterobiasis.[9, 10] In our study we did not examine any stools for the presence of pinworms; however, all patients were carefully observed for the presence of pinworms at the anal orifice by the nurses in the hospitalized patients and by the parents in the clinic cases. In our opinion the presence of viable eggs found by the Scotch tape smear technique seven days after the cessation of treatment proves the presence of unharmed gravid adult female worms that are still capable of spreading the infection or reinfecting the host. In many instances the smears we examined still showed embryonic motility even on the seventh post-treatment smear and some of these still showed motility even when re-examined two days after the smears were obtained. Even if papain completely digests the parasite as reported by Weise in his vitro and vivo studies, the presence of viable eggs seen seven days after treatment indicates that either the enzyme does not penetrate the three layers of the worm eggs or that not enough of the worms are digested, partially or wholly, by the enzyme. In either case the possibility of reinfection and spread of infection remains a real threat in the control of pinworm infection.

In our study, we were able to confirm the observations of Weise, that papain is completely harmless and that the patient's general well-being is not unfavorably influenced by the treat-

ment. In no cases was any unfavorable reaction observed. If Weise's high percentage of cures with papain could be confirmed, the complete absence of any unfavorable reaction and the very low cost would make papain the ideal oxyuricide.

SUMMARY

Although the number of cases reported in this study is small, it is our opinion that papain falls short of being the ideal drug for the treatment of pinworm infection. The percentage of cures, 10 per cent, obtained in our study is considerably less than that obtained with the already better known oxyuricides.

We have been able to comfirm the report of Weise, as reported in the German literature, that papain* is a nontoxic and completely safe vegetable enzyme.

*Papain was provided by Eli Lilly & Co., Indianapolis, Ind.

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THE USE OF THE ELECTROPHRENIC RESPIRATOR IN THE MANAGEMENT OF RESPIRATORY DIFFICULTY IN POSTMEASLES ENCEPHALITIS

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THE management of the acute stage of postmeasles encephalitis may present a variety of difficult problems. Steady progression to death occurs in some cases in spite of the use of all types of "supportive therapy."

Death may occur in several ways in the postinfectious encephalitides: (1) In the stuporous or comatose patient there is the constant danger of the development of a complicating bacterial pneumonia. This may be initiated by the accidental aspiration of pharyngeal secretions or vomitus, or not infrequently may appear without the intervention of either of these accidents. (2) Continued intractable convulsions occasionally occur. Although they may not respond at first to such measures as the administration of barbiturates, paraldehyde, or magnesium sulfate, the seizures can usually be brought under temporary control by general anesthesia. The primary aim in this situation is to stop the convulsions for periods long enough to allow normal effective breathing, so that the cerebral damage incident to prolonged periods of hypoxia may be prevented. Phenobarbital together with regular administration of Dilantin is often effective in preventing the reappearance of seizures once they have been stopped. (3) Occasionally children die in the acute phase of postmeasles encephalitis shortly after developing the syndrome of shock. This may appear within a short time after the onset of the first signs of the disease. The clinical picture resembles very closely that observed in patients who have bulbar poliomyelitis with disease of the medulla and who expire rapidly. This syndrome in measles is probably due to the same mechanism as the one operative in infantile paralysis—involvement of the vasomotor centers. (4) A number of patients in the early period of postinfectious encephalitis display irregular breathing similar to that seen when the respiratory center is affected during the course of bulbar poliomyelitis. The respiratory embarrassment is characterized by complete irregularity of spacing and depth of respiration, and varies from a degree so minor that no specific treatment is required to a severity in which complete respiratory failure is followed by death.

When respiratory center involvement supervenes in the course of postmeasles encephalitis, oxygen must always be given, although, in itself, it produces little improvement unless the ventilatory difficulty is only slight. Because of the gross irregularity of breathing, the ordinary measures of artificial respiration, including the tank and chest type respirators, are of

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little or no value. The clinical picture seen in postinfectious encephalitis impressed us with its resemblance to that which occurs when the respiratory center is damaged in the course of poliomyelitis. As the electrophrenic respirator has been widely applied with considerable success in the management of poliomyelitis[1] its use in patients with encephalitis following rubeola who appeared to be suffering from dysfunction of the respiratory center suggested itself. The purpose of this paper is to describe four patients with postmeasles encephalitis in whom marked irregular breathing was present in severe degree, and who were successfully treated by the application of electrophrenic respiration.

CASE REPORTS

CASE 1.—G. D., an 8-year-old white boy, was admitted to the Haynes Memorial Hospital because of convulsions lasting for six hours. Five days before entry he developed typical measles which was apparently running an uneventful course. On the day of admission, under unknown circumstances, the patient fell from a bed on which he was standing and shortly thereafter began to have a generalized seizure. The family physician who was called to see him administered phenobarbital parenterally. Because twitching movements persisted despite the therapy, the child was referred to the hospital. At the time of admission he appeared severely ill and was in the throes of a generalized clonic seizure. The temperature was 101.2° F. (R), the pulse 140, and respiratory rate 36 per minute. The blood pressure was 110/60. Important physical findings included a fading morbilliform eruption over the face, trunk, and extremities, moderate stiffness of the neck, hyperactive but equal deep tendon reflexes, and poorly sustained ankle clonus bilaterally. The lungs and heart appeared to be normal.

Laboratory studies at the time of admission showed a hemoglobin of 14 grams per 100 ml. The hematocrit was 43 per cent. The white blood count was 29,950 with 79 per cent neutrophils, 19 per cent lymphocytes, and 2 per cent monocytes. Lumbar puncture revealed clear fluid under normal pressure; it contained 11 lymphocytes per cubic millimeter, 115.2 meq. per liter of chloride, 21 mg. of protein, and 77 mg. of sugar per 100 ml. Cultures of the throat revealed no pathogens. The blood and cerebrospinal fluid were sterile.

When the patient entered the hospital a large collection of fluid in the pharynx was aspirated and he was given oxygen. Since he was still undergoing a severe convulsion despite barbiturate therapy he was given ether by open mask until the seizure stopped. Within a few minutes after cessation of the ether intense clonic movements started once more and were again controlled by light anesthesia. Although seizures did not return, it was noted that the respirations had become markedly irregular in depth and spacing, with periods of apnea lasting as long as ten seconds. Electrophrenic stimulation, using the finger-cot electrode, was instituted shortly after the respiratory irregularity appeared and was continued intermittently for about one hour. At the end of this time, breathing was completely regular without the aid of the respirator. Facial asymmetry and a nasal quality of the voice became apparent on the second hospital day but gradually cleared. Silly behavior was manifested after about one week of hospitalization but this too disappeared. The child eventually recovered completely without obvious neurological or psychiatric sequelae and was discharged from the hospital twenty-two days after admission.

CASE 2.—S. C., a 5-year-old girl, became ill with cough, coryza, fever, and malaise one week before admission to the hospital. She developed a typical morbilliform skin eruption and the

diagnosis of measles was made by her physician. She got along well until one day prior to hospitalization when there was an increase in her cough and a rise in the temperature which had been falling toward normal. On the day of admission the patient rapidly became unresponsive and had two short convulsions which were characterized by rigidity, slight shaking movements, clenching of the teeth, gasping respiration, and transient cyanosis. The past history was irrelevant except that the child had not had measles previously and at the age of 18 months contracted pulmonary tuberculosis for which she spent three years in a hospital.

Physical examination at the time of admission revealed a comatose youngster with a temperature of 104.6° F. (R), pulse of 140, and respiratory rate of 30 per minute. The blood pressure was 110/60. There was a fading morbilliform eruption with many small hemorrhagic areas. Dullness to percussion, coarse breath sounds, and moist râles were detected at the right lung base posteriorly. There were scattered rhonchi throughout the rest of the chest. The neck was moderately stiff. The pupils were dilated and fixed. All of the superficial and deep tendon reflexes were absent. Plantar response was extensor bilaterally.

Laboratory studies revealed a hemoglobin of 14.2 grams per 100 ml., an hematocrit of 40 per cent, and a corrected sedimentation rate of 41 mm. per hour (Wintrobe). The white blood count was 17,100 with 80 per cent neutrophils and 20 per cent lymphocytes. Urinalysis revealed no abnormalities. The blood nonprotein nitrogen, chloride, and CO_2 content were normal. Examination of the cerebrospinal fluid showed 620 white blood cells per cubic millimeter; of these 90 per cent were lymphocytes. The spinal fluid contained 50 mg. of protein and 104 mg. of sugar per 100 c.c.; the chloride content was 130.4 meq. per liter. Culture of the throat yielded predominantly hemolytic *Staphylococcus aureus* and *Hemophilus influenzae* as well as a small number of *Streptococcus viridans*. Blood and spinal fluid were sterile. Roentgenographic study of the lungs disclosed interstitial infiltration with segmental collapse of the right lower lobe.

Treatment immediately after entry to the hospital consisted of the administration of penicillin and streptomycin intramuscularly, parenteral fluids, oxygen, and Dilantin. By the morning of the third hospital day, the patient was afebrile and was able to respond to simple questioning, and answer when her name was called. On the afternoon of that day, the temperature rose rapidly to 104° F. and shortly thereafter a generalized clonic seizure occurred. Following this convulsion, respiration became very irregular and ineffectual. Phenobarbital was administered subcutaneously and electrophrenic respiration, using the finger-cot electrode, was initiated. Adequate pulmonary ventilation was maintained by this method for about four hours. After this time breathing was established in a normal effective pattern and remained so during the remainder of the hospital stay. One mild convulsion, without respiratory difficulty, occurred the next day. Following this there were no further seizures. Progressive improvement continued and the patient was discharged from the hospital fifty-four days after admission.

CASE 3.—G. C., a 6-year-old white boy, was admitted to the Haynes Memorial Hospital because he had had convulsions continuously for three hours and was in a coma. Nine days before admission, the patient developed measles. He became afebrile by the fifth day and was getting along so well that he was allowed out of bed on that day. Four days later, he appeared somewhat listless but was otherwise normal. In the afternoon, however, he suddenly began to froth at the mouth, vomited, and began to have generalized tonic-clonic-tonic seizures.

He was seen by his family physician who found him to be convulsing and comatose. He administered a barbiturate intrarectally and sent him to the hospital.

Physical examination at the time of admission revealed a stuporous boy with markedly irregular and apparently ineffective respiration as evidenced by the presence of a varying degree of cyanosis. The temperature was 101.6° F. (R), the pulse was 150, and respirations 30 per minute. The blood pressure was 130/70. There was a fading morbilliform rash covering the entire body. The neck and back were supple and the Kernig sign was negative. The lungs were normal except for widely distributed coarse breath sounds. None of the deep or superficial reflexes could be elicited.

The hemoglobin was 14 grams per 100 c.c. and the hematocrit 40 per cent. The white blood count was 22,800 with 83 per cent neutrophils and 17 per cent lymphocytes. Examination of the urine revealed no abnormalities. Lumbar puncture was omitted because of the gravity of the clinical condition.

Shortly after admission the patient had a severe convulsion involving the right arm, right leg, and the left side of the face, during which he vomited a moderate amount of brown material containing altered blood. Sodium phenobarbital was injected intramuscularly but the seizures steadily increased in intensity. The convulsion was finally stopped by induction of anesthesia with ether. Additional treatment consisted of nasal oxygen, intramuscular penicillin and streptomycin, and intrarectal Dilantin. Because of the very poor quality of the breathing, electrophrenic respiration was applied for about three hours. After this period, respiration, though not completely regular, was much improved and ventilation appeared to be adequate. From this point, improvement was rapid. Seven hours after admission, breathing was normal and the youngster was responsive and able to take fluids orally. The remainder of the hospital course was uneventful and the patient was discharged apparently recovered on the nineteenth day.

CASE 4.—C. S., a 4-year-old white boy, was well until six days prior to admission to the hospital. At this time it was first noted that he had a cough and a slight coryza. Three days later he developed a typical measles eruption accompanied by fever and aggravation of his previous symptoms as well as severe epistaxis. He appeared to be recovering uneventfully until early on the morning of the day of admission when he complained of generalized abdominal pain. The family physician was called and shortly after his arrival, the child began to have a generalized clonic convulsion with dyspnea and cyanosis. Large doses of phenobarbital were given parenterally without effect and hospitalization was advised.

On admission to the hospital the child showed localized twitchings which rapidly progressed to generalized tonic-clonic seizures. Respiration was markedly irregular and there was moderate cyanosis. The temperature was 103.2° F. (R), the pulse was 150, and the respiratory rate could not be determined accurately because of its rapidity and irregularity. The skin revealed a generalized morbilliform rash with many punctate hemorrhages. There were numerous loud rhonchi throughout the chest. The pupils were dilated, the left being smaller than the right. The neck and back were supple and the Kernig sign was negative. The abdomen was distended, tympanitic, and peristaltic noises could not be detected. The corneal reflexes were absent on both sides. The deep and superficial reflexes could not be obtained. The plantar response was absent on the left and flexor on the right. There appeared to be weakness of the left arm and leg.

The hemoglobin was 14.5 grams per 100 c.c. and the hematocrit 41.5 per cent. The white blood count was

20,400 with 60 per cent neutrophils (30 per cent immature forms), 36 per cent lymphocytes, and 4 per cent eosinophils. The platelets appeared to be decreased in number on a Wright-stained smear. The urine gave a 3+ reaction for ketones. The cerebrospinal fluid was under normal pressure and contained 15 erythrocytes, 4 neutrophils, and 61 lymphocytes per cubic millimeter. The protein content was 39 mg. and the sugar 112 mg. per 100 ml. The peripheral white blood count fell to 10,100 on the second day and remained normal thereafter. Blood nonprotein nitrogen, glucose, sodium, potassium chloride, and CO_2 content were all normal.

Because of the extreme irregularity and ineffectiveness of the breathing as evidenced by high-grade cyanosis, treatment with the electrophrenic respirator, using the finger-cot electrode, was instituted immediately after the patient was admitted to the hospital. The convulsions were controlled by the inhalation of ether. Additional therapy consisted of nasal oxygen, intramuscular injection of a combination of penicillin and streptomycin, intrarectal injection of Dilantin, and the administration of parenteral fluids. A large amount of air and dark brown fluid containing blood was removed from the stomach by tube. Although many attempts were made to stop electrophrenic respiration, markedly irregular and totally ineffective breathing reappeared almost simultaneously with interruption of electrical stimulation of the phrenic nerve. It required about nine and one-half hours before electrophrenic respiration could be stopped. Even after this time, although ventilation was apparently adequate, the respirations were still somewhat irregular and continued so for several more hours. Coma persisted during the next five days and occasional short seizures, several of which were focal in nature, were noted during this period. From that point on, there were no further seizures, respirations remained completely regular and adequate, and there was slight improvement in the general clinical condition. At the time of this report the patient is able to take fluid and food by mouth, and moves actively about in bed. However, he has incontinence of urine and feces, chews his arms and hands, and is apparently both blind and deaf.

DISCUSSION

The four patients described in this paper all presented a marked degree of respiratory irregularity apparently due to involvement of the respiratory center during the acute phase of postmeasles encephalitis. Although accurate determinations of the arterial oxygen saturation were not made, the degree of ventilatory impairment in each instance appeared, on clinical grounds, to be great enough to jeopardize the patient's chance for survival. In two cases (C. S. and G. C.) past experience indicated strongly that neither could have survived without the help of the electrophrenic respirator. In every instance the institution of electrophrenic respiration resulted in an immediate effect and permitted the maintenance of adequate gas exchange until normal regulation of breathing could again become established.

One of the most striking features of the respiratory difficulty in postmeasles encephalitis was its relatively short duration when properly treated. The observations recorded in this paper indicate that irregularity of breathing in this disease may persist for as little as one hour. Even as short a time as this, however, may seriously compromise the possibility of survival if the respiratory irregularity is of high degree. This situation differs somewhat from that which develops during the course of involvement of

the respiratory center in bulbar poliomyelitis where ventilatory difficulty may and often does persist for many hours or even several days if the patient survives. In measles encephalitis as well as in poliomyelitis, once regular respiration has appeared and been maintained for even a short while, irregularity does not return. The beneficial effect of electrophrenic respiration in both diseases is very similar.

It is very probable that many of the fatalities that occur in the early phase of postmeasles encephalitis are due to mild functional derangement followed by complete loss of regulation of breathing by the respiratory center. Although death may result from other causes, with the exception of severe, intractable convulsions, these usually develop later in the course of the disease. The clinical recognition of respiratory center involvement is simple. The presence of marked irregular respiration in the presence of completely normal muscles of respiration establishes the diagnosis. It is important that this disturbance be recognized promptly and effective electrophrenic respiration applied immediately. Since convulsions appear to be an almost constant predecessor or concomitant finding at the time of respiratory irregularity, treatment to stop them must be carried out simultaneously with institution of adequate ventilation. In our experience phenobarbital parenterally in a dose adjusted to the body weight of the patient suffices to terminate the acute seizure in a short time in most cases. It has been the practice to administer Dilantin at the same time and to continue its use for five or six days after convulsions have stopped. Oxygen has always been given. In instances where barbiturate is ineffective and the patient is in status epilepticus, anesthetization by the inhalation of ether, although it may require repetition, is frequently effective when all other measures have failed.

CONCLUSIONS

1. Four patients with involvement of the respiratory center during the acute phase of postmeasles encephalitis are described.

2. In each instance the application of electrophrenic respiration allowed the maintenance of an adequate degree of ventilation.

3. The duration of the respiratory irregularity in postmeasles encephalitis is usually short and, if the patient can be tided over for a few hours, normal breathing is resumed.

4. There is no recurrence of respiratory irregularity once normal breathing has been established.

5. The electrophrenic respirator is a very valuable adjunct to the limited therapeutic armamentarium available for the management of the postinfectious encephalitides. Its proper use is unquestionably lifesaving.

6. In patients who have respiratory irregularity and convulsions simultaneously, it is of greatest importance to control and stop the seizures.

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INFANTILE CORTICAL HYPEROSTOSIS (CAFFEY-SMYTH SYNDROME)

Report of a Case in a Negro Infant

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Washington, D. C.

INFANTILE cortical hyperostosis was first described in 1930 by Roske[1] who reviewed the case of a male infant with widespread deposits of subperiosteal bone about the extremities and mandible. In 1945 Caffey and Silverman[2] presented four cases of a new syndrome, the findings being quite similar to the case of Roske. One year later Smyth, Potter, and Silverman[3] reported seven children whom they considered as belonging to the same group as Caffey's cases. Since 1946 about forty additional cases have been reported.[4]

CASE REPORT

B. R., a 7-month-old Negro female infant, was seen by us because of remittent swelling of the face for a period of three months. The infant was a full-term normal baby at birth, weighing 6 pounds 8 ounces. Delivery was spontaneous and by cephalic presentation. The mother, aged 18 years, had begun her prenatal care during the sixth month of gestation. The prenatal course was entirely uneventful and she was kept on a fairly well-balanced diet including one quart of whole milk per day. No supplementary vitamins or iron were given, however. There was no history of infectious disease or disease contacts during the pregnancy. Labor lasted twenty-four hours.

The infant was breast fed for one and one-half months after which time an evaporated milk formula was tolerated well. Vi-Syneral vitamin drops were started at 2 months of age in a dosage of 6 drops per day. She received orange juice at 4 months of age but this had to be discontinued because of an allergic rash. Strained foods were taken well after the second month. Meat and eggs were added at 5 months.

The mother first noticed progressive swelling of the infant's face at the age of 4 months. This was accompanied by fever for about one week at the onset. Irritability was marked and excess crying was noted when the right arm was manipulated or when either side of face was touched. At this time the infant was taken to another hospital where penicillin was given and the mother advised to discontinue the

Fig. 1.—Showing symmetrical and diffuse swelling of face and jaws. There was no hyperemia or increase in local heat.

From the Department of Pediatrics, Howard University School of Medicine and Pediatric Service of Freedmen's Hospital.

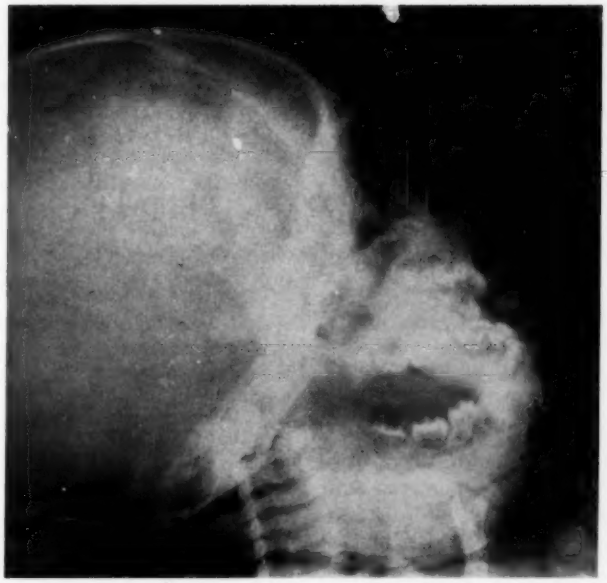

Fig. 2.—Showing thickening and sclerosis of the mandible.

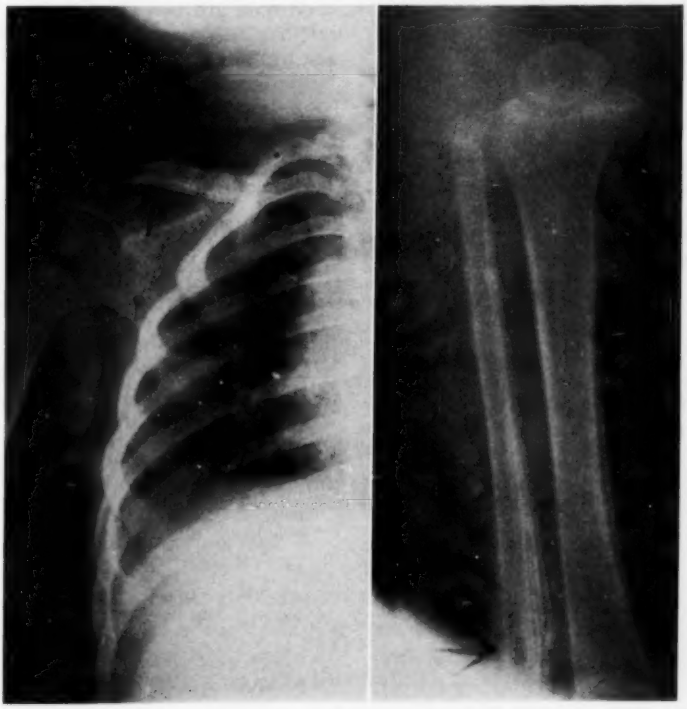

Fig. 3.—Early manifestations of cortical hyperostosis involving the clavicle and distal portions of the tibia and fibula. There was also slight involvement of each ulna.

Vi-Syneral. During the following months the facial swelling subsided somewhat but recurred at the age of 6 months.

The infant's motor development was not unusual. She held her head upright at 3 months and sat alone at 7½ months. The patient's first tooth erupted at 4 months of age. At present, at age of 8 months, she has six incisors.

Physical examination at the age of 7 months revealed a fairly well-developed, moderately undernourished female infant. The most obvious physical finding was the marked, brawny swelling of both cheeks and submental areas which did not appear tender (Fig. 1). There was no increased local heat, redness, or fluctuation. The remainder of the physical examination revealed essentially normal findings. Roentgen survey of the entire skeleton showed hyperostosis of the mandible (Fig. 2) and scattered cortical reaction of both upper and lower extremities (Fig. 3). The scapulas did not appear to be involved. The hemogram and urinalysis revealed essentially normal findings. The serological test for syphilis and the intradermal tuberculin test were negative.

During the past two months the infant has shown some improvement. The facial swelling is subsiding and her general condition is good. No specific treatment has been given.

COMMENT

Infantile cortical hyperostosis begins during the first six months of life. The disease is characterized by fever and irritability with swelling of the face and extremities. There may be exacerbations and remissions. X-ray examination reveals cortical thickening of the mandible. Other bones most commonly involved are the tubular bones of the extremities, the ribs, scapulas, and clavicles. Bones of the hands and feet are not affected as a rule. There are no specific pathological findings.[5] Prognosis is good for complete recovery despite there being no known effective treatment. In the differential diagnosis one must exclude other diseases which may involve the osseous system of infants such as scurvy, syphilis, tuberculosis, and pyogenic osteomyelitis. Vitamin A poisoning may simulate infantile cortical hyperostosis but can be excluded on the absence of fever, presence of elevated vitamin A in the blood, and onset after twelfth month of life.

SUMMARY

A case of infantile cortical hyperostosis in a Negro infant has been presented. The cardinal features of this syndrome are briefly reviewed. There is no effective specific treatment but the prognosis is uniformly good in the mild cases.

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A NEW INFUSION VALVE

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THE most popular and efficient method of administering intravenous blood and other intravenous therapeutic fluids to infants and small children is that of injection of the fluids by using a 10 c.c. Luer-Lok syringe and a three-way stopcock. The administration of intravenous fluids in babies by the drip method has many obvious disadvantages, particularly in the outpatient. The utilization of small superficial veins as those in the scalp, hands, and feet have proved satisfactory when the therapeutic fluid is injected slowly with a 10 c.c. syringe and a three-way stopcock.

The difficulties encountered with the three-way stopcock when the injection method is used has prompted the dedevopment of a new "infusion valve." The core of the three-way stopcock must be turned following the injection of a syringeful of fluid and again it must be rotated following the filling of the syringe. Therefore, the stopcock must be manipulated twice for each 10 c.c. of fluid administered. The manipulation often leads to getting out of the small vein. The core of the three-way stopcock is held in place by a set-screw on the bottom of the stopcock. If this screw is too tight the core is difficult to turn; if too loose, then the fluid being given leaks as it is being injected. Also, air occasionally enters system.

A drawing of the new valve is shown in Fig. 1. Two ball valves which work opposite each other offer an infusion valve which permits filling of syringe and injection of fluid by merely pushing and pulling the piston of the syringe. A photograph of this valve assembled for use is shown in Fig. 2.

In preparing to give an intravenous infusion, one should fill a 10 c.c. Luer-Lok syringe one-half full with saline and then apply the syringe to the infusion valve. The tubing from the fluid reservoir should be filled with the therapeutic fluid, clamped off, and then inserted into the side arm of the infusion valve. A 23 or 22 gauge needle

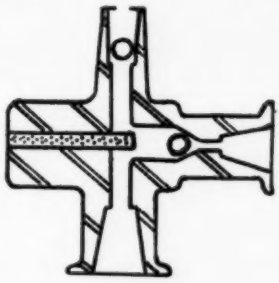

Fig. 1.

is attached and a small amount of saline is injected through the valve to displace any air present. Once the vein is entered, the clamp should be released from the fluid tubing and the infusion can then be given by merely pushing and pulling the plunger and without further manipulation. One cannot aspirate with this valve. The purpose of the saline in the syringe is for determining whether one is in the vein by test injection. In superficial

From the Children's Clinic.

veins this method is preferable to aspiration and is universally practiced.

This new infusion valve has been used successfully in twenty-six intravenous infusions, and it is noteworthy that during this series, each infusion was completed by entering only one vein. It has also been found to be of value in gastric lavage in children who have ingested a poison. Here the lavaging fluid can be injected conveniently from the fluid reservoir by using the transfusion valve. It has also been an aid in exchange transfusions. In this case, one three-way stopcock and two infusion valves are used in series. One valve is used in administering the blood and the other for withdrawing blood.

Fig. 2.

The valve also may be used in continuous intravenous infusions. The setup is identical with the one used in the injection infusion as described above and the plunger is secured in the syringe with the aid of adhesive tape. This arrangement allows one to give fluid intermittently by injection as needed during the continuous drip.

The proper cleaning of this valve was studied thoroughly prior to its clinical use. The valve was allowed to stand in oxalated blood for a period of one hour and then left in open air to dry for another hour. It was then rinsed with tap water and boiled in soapy water for ten minutes. This process was carried out on a valve made of stainless steel and also on one made of brass. Following the boiling in soapy water both valves were opened for inspection. The stainless steel valve was completely clean throughout, while the one of brass cleaned less well because of tarnished areas on the metal. In addition, one stainless steel valve was opened for inspection after its use in twenty-five blood transfusions. This valve also was found to be clean.

This device is made of stainless steel throughout. It should be cleaned immediately after use by forcibly aspirating and ejecting water through it several times with the aid of a syringe. This is all that is necessary in cleaning it following its use with such solutions as glucose, saline, and sodium lactate. However, following its use with blood, it is recommended that the valve be boiled in soapy water and then rinsed copiously with tap water prior to sterilization.

SUMMARY

A new valve for intravenous infusions in pediatric patients has been presented. This valve functions on the basis of two reciprocating ball valves. It is also of aid in gastric lavage and exchange transfusions.

The authors wish to acknowledge the assistance of Mr. Edward A. Dutt, Jr., in the construction of this valve.

MYOCARDITIS OF UNKNOWN ETIOLOGY (FIEDLER'S?) TREATED WITH ACTH

Report of a Case in a 7-Year-Old Boy With Improvement

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THE purpose of this report is to record a case of possible idiopathic myocarditis which apparently improved under treatment with ACTH. It is appreciated by the authors that in the past this diagnosis has been established only by autopsy studies. We feel that the diagnosis is justified in this case since other possible diagnoses such as rheumatic myocarditis, idiopathic cardiac hypertrophy, toxic and infectious myocarditis, beriberi, and potassium deficiency effect were excluded by history, clinical course, and laboratory findings.

Idiopathic myocarditis was first described by Fiedler[1] in 1899 and is known by several terms, such as Fiedler's myocarditis, isolated myocarditis, and interstitial myocarditis. Since that time a number of reports have been made on the basis of autopsy findings and mostly in small infants.

This is the first reported case of ante-mortem diagnosis and attempt at treatment with ACTH.

CASE REPORT

A white boy 7 years of age was admitted to the University of Kansas Medical Center on June 16, 1951. He had been well until one week prior to admission at which time he had sudden onset of a cough. The cough was harsh, nonproductive, and worse in the early morning. Two days prior to admission the child also complained of shortness of breath on exertion, associated with right upper quadrant abdominal pain. On the day prior to admission the patient was seen by his private pediatrician who noted right upper quadrant tenderness and possible slight icterus. A third heart sound was also noted. Admission physical examination at this time revealed a boy with sallow complexion who did not appear acutely ill. His blood pressure was 100/60; pulse, 130; and temperature, 98° F. Abnormalities on examination were inspiratory piping râles over the left lower lobe of the lung and occasional expiratory râles. The patient had a harsh, abrupt, bronchial cough. Examination of the heart showed the P.M.I. to be in the fifth interspace outside the mid-clavicular line. A gallop rhythm was present with three distinct heart sounds. In the pulmonic area the first sound was muffled and the second sound was loud and snapping. No definite murmurs were present. There was right upper quadrant abdominal tenderness, but the edge of the liver was not definitely felt.

Laboratory data showed the urine, blood count, and serology to be normal. A hepatogram, including serum bilirubin, total protein, albumin-globulin ratio, and cephalin flocculation, was normal. No unusual flora was found in the nose and throat on culture. An electrocardiogram revealed a sinus tachycardia, a rate of 160, and marked right axis deviation. The P-R interval was normal. T waves were flattened throughout. X-ray of the chest was read as showing pneumonia in the right base and cardiac enlargement, probably primarily right heart. The patient was treated with penicillin and aureomycin with little improvement. The temperature was 98° F. on admission with occasional elevations not to exceed 99.6° F. during hospitalization. He was dismissed on the

*840 Argyle Bldg.

fourth hospital day with a diagnosis of atypical pneumonia and sinus tachycardia of unknown etiology. It was felt that the child possibly had a myocarditis secondary to the pneumonia, so he was closely watched by his private physician in the interval after dismissal.

The following week the child was very anorectic and had severe abdominal pain and nausea; no vomiting occurred except that which the patient induced himself for relief. The tachycardia persisted and an electrocardiogram on June 28, 1951, showed a rate of 140 and flat T waves. Fluoroscopy on that date revealed marked cardiac dilatation and the patient was readmitted to the University of Kansas Medical Center.

On this second examination the boy appeared acutely ill. His temperature was 98.8° F.; pulse, 144; respiration, 36; blood pressure, 85/55. The neck veins seemed slightly more prominent than normal and the chest showed prominent superficial veins. The lung fields were clear to auscultation and percussion. The heart revealed the P.M.I. visible in the sixth interspace in the anterior axillary line. By percussion the heart appeared to be enlarged slightly to the right and downward to the sixth interspace in the anterior axillary line. The gallop rhythm was still present. There was tenderness in the right upper quadrant and the liver seemed enlarged although no definite edge was felt. The clinical impression on the second admission was acute myocarditis (etiology to be determined) and incipient cardiac failure.

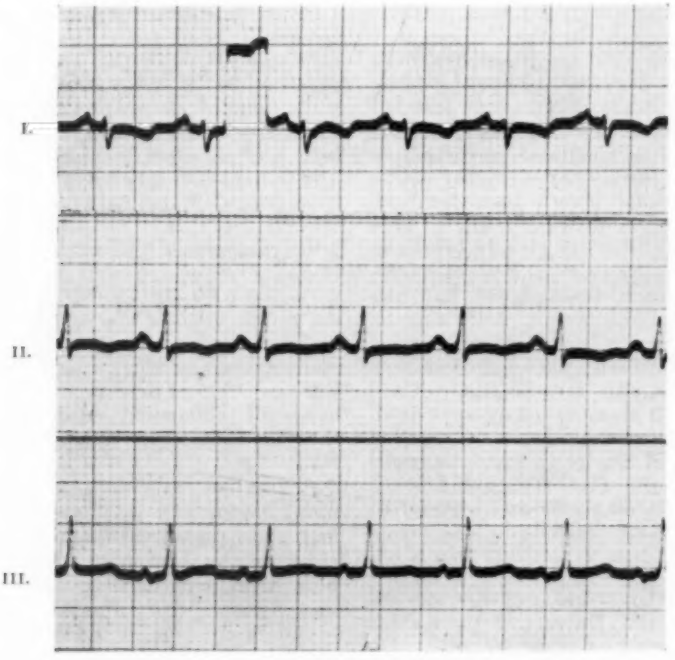

Fig. 1.—Electrocardiogram taken July 2, 1951, before ACTH therapy.

Laboratory examinations revealed a normal blood count and urinalysis. Admission sedimentation rate (Cutler method) was 0 mm. per hour. Subsequent sedimentation rates were 1.7

mm. per hour on July 3, 1951; 1 mm. per hour on July 15; 1 mm. per hour on July 18. Hematocrit was 40.5 per cent. All blood cultures were negative. Nonprotein nitrogen of the blood was 46 mg. per cent; repeated, 36.5 mg. per cent. Fasting blood sugar was 86 mg. per cent; serum Na, 146 meq.; serum Cl, 102 meq.; serum K, 5.9 meq. The Thorn test was done, showing a base line of 294 circulating eosinophils per cubic millimeter; four-hour specimen, 88 eosinophils per cubic millimeter; six-hour specimen, 44 eosinophils per cubic millimeter. Repeated blood electrolyte studies showed no unusual change during the hospital course. Antistreptolysin 0 titers were as follows: on admission, 125 units; July 18, 100 units. Antihyaluronidase titers showed on admission a titer of 1:512; July 18, 1:512; July 31, 1:256 (measured against sixteen units of group A, type 4 streptococcus). An electrocardiogram on July 2 (see Fig. 1) showed persistent sinus tachycardia and unusual T-wave configuration, nonspecific, but suggestive of some type of myocardial dysfunction. The right axis deviation was not considered unusual for the age. Two days later the T wave had become more inverted, particularly in Lead I. Cardiac fluoroscopy and posteroanterior and lateral x-rays (see Fig. 3) of the chest on admission revealed generalized cardiac enlargement, poor muscle tone, and moderate decompensation. The roentgenologists felt in retrospect the original diagnosis on the first admission should have been cardiac decompensation instead of pneumonia.

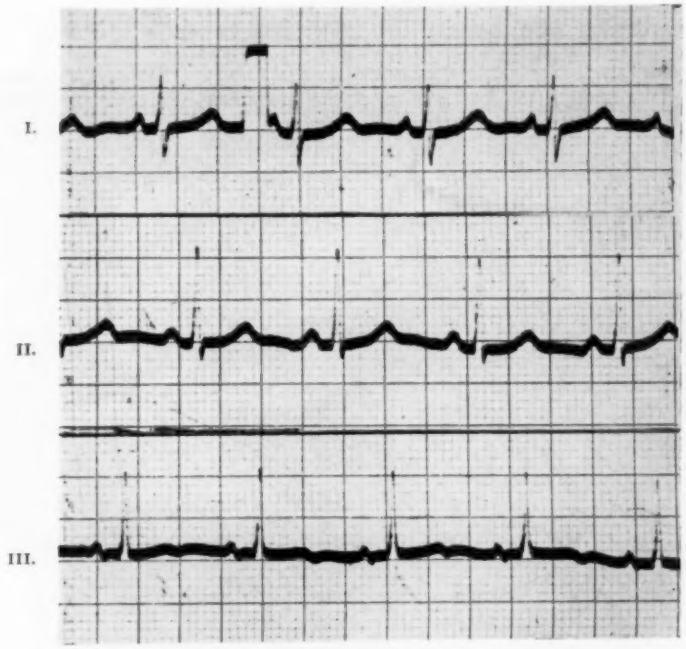

Fig. 2.—Electrocardiogram taken July 13, 1951, after ACTH therapy.

Hospital course: On admission the patient was placed on strict bed rest and aqueous penicillin parenterally. During the next three days his condition became progressively worse with increasing dyspnea and slight cyanosis,

even at rest. Administration of continuous oxygen resulted in some improvement with slowing of the pulse from 140 to 120 beats per minute and disappearance of the gallop rhythm. On July 2, administration of ACTH, 100 mg. daily in divided doses intramuscularly, was initiated. Within the next forty-eight hours the heart rate had slowed to 100, the rhythm was regular, and the intensity of the cardiac tones was improved. A systolic mitral murmur was audible and the liver was tender but the edge could not be felt definitely. The patient had shown no increase in weight and no peripheral edema, but it was felt advisable to digitalize him at this time. This was accomplished during the next four days by oral digitoxin. By July 6 the child had shown marked clinical improvement with slowing of the heart rate to 80 beats per minute and increase in appetite. He had gained 2½ pounds. of weight since the start of therapy. Electrocardiogram and x-rays at this time showed no significant changes from those taken on admission, however. The ACTH was decreased on this date to 60 mg. daily in divided doses and the digitoxin was continued. Clinical improvement continued and by July 11, the liver was no longer tender and the lungs were clear. Digitalis was discontinued. On July 13 the electrocardiogram (see Fig. 2) interpreted to be within normal limits and starting on the following day, the twelfth day of ACTH therapy, the dosage was reduced to 40 mg. and then decreased every two days to 20, 10, and 5 mg. daily. ACTH was discontinued on July 23 after twenty-one consecutive days of therapy.

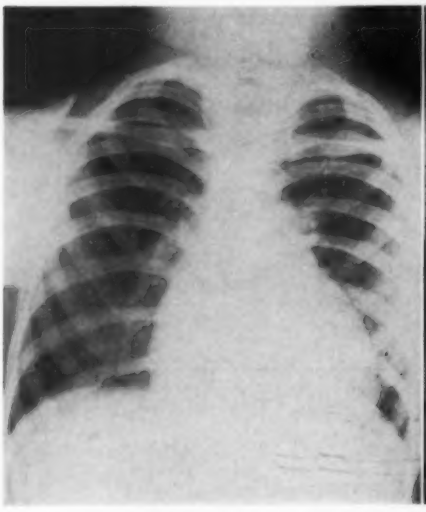

Fig. 3.—X-ray taken July 2, 1951, before ACTH therapy.

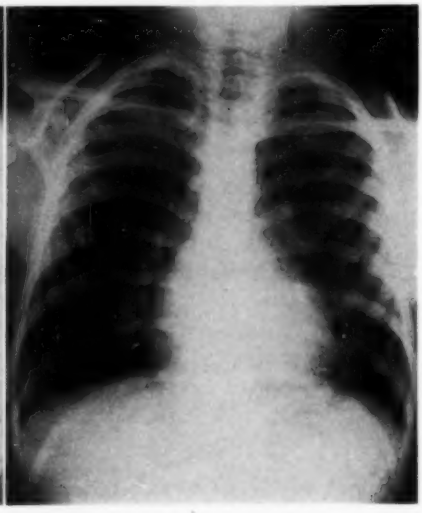

Fig. 4.—X-ray taken July 25, 1951, after ACTH therapy.

Response to ACTH therapy was followed by daily circulating eosinophil counts. The count dropped from 255 eosinophils per cubic millimeter on the day prior to ACTH therapy to 0 eosinophils per cubic millimeter on the third day of therapy. Thereafter the daily count ranged from 0 to 17 eosinophils per cubic millimeter during the period of therapy and rose to 444 eosinophils per cubic millimeter after discontinuance of ACTH.

On July 25 fluoroscopic examination of the chest revealed normal heart contour and size with relatively normal cardiac pulsation (see Fig. 4). Hilar

shadows were a little exaggerated but the lung markings were essentially normal. An electrocardiogram showed no abnormalities and clinically the patient presented no abnormal findings. The patient had assumed a slightly moon-shaped face and slightly obese-appearing abdomen but no other side effects of ACTH were noted. He remained afebrile during the hospitalization. The remainder of the hospital and he was hospitalized for the third time on Sept. 18, 1951.

On his third (hospital) admission (this time at St. Mary's Hospital, Kansas City, Mo.) his presenting complaints were the same, abdominal and back pains. His pulse rate was 148 and a soft systolic murmur was heard over the precordium. There was fullness noted of the upper abdomen but again a definite liver edge could not be felt.

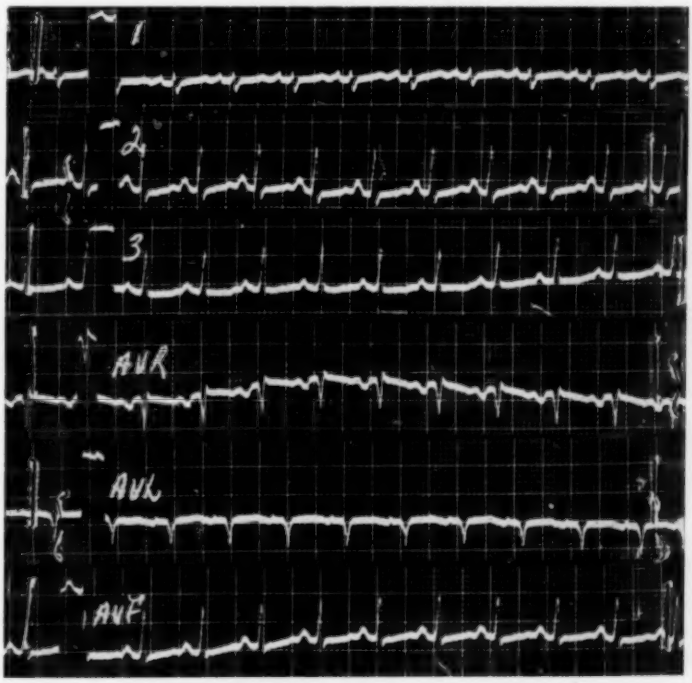

Fig. 5.—Electrocardiogram on Sept. 19, 1951, when the patient had a relapse.

course was uneventful and the patient was dismissed on Aug. 6, 1951, the fortieth hospital day to be followed at weekly intervals and to be kept at bed rest at home. The weight on discharge was 53 pounds, three-fourths pound less than on admission.

After discharge he was evaluated weekly. For one month his cardiac size and electrocardiogram remained normal. Then his tachycardia returned No râles were heard in the chest. Routine blood and urine studies were normal. The Cutler sedimentation rate was 4.5 mm. The electrocardiogram (Fig. 5) on September 19 again was abnormal, showing T-wave changes and right axis deviation. The chest x-ray taken on the same day showed marked cardiac dilatation and bilateral congestive changes. He was again placed on ACTH and digitalis with

marked clinical improvement in a few days. The electrocardiogram showed some improvement two days later (Fig. 6) and was essentially normal (Fig. 7) by October 1. The heart rate rapidly returned to normal, and on September 25 the x-ray showed the heart size to be much smaller and there was clearing of the lung fields. His murmur disappeared, he resumed a sense of well-being and was discharged on Oct. 6, 1951. Again at no time did he develop fever.

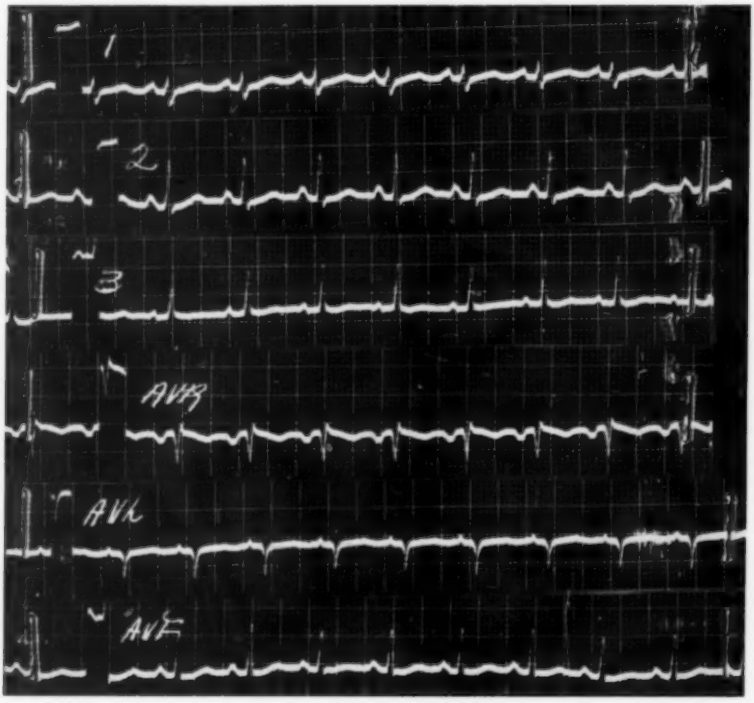

Fig. 6.—Electrocardiogram on Sept. 21, 1951, following two days of ACTH therapy.

This time upon discharge he was placed on a maintenance dose of ACTH (12.5 mg.) every other day by subcutaneous injection. Also a small maintenance dose of digitalis was given. He was followed at monthly intervals. The electrocardiogram has remained within normal limits, and the chest x-ray showed decreasing heart size with normal lung fields. Blood counts, urinalyses, and sedimentation rates have remained normal. His physical activity has been gradually resumed and he is symptom free. The last examination by the cardiologist on Sept. 3, 1952, showed no murmurs, normal electrocardiogram, and normal heart size by x-ray. He is attending school and complains now only of hay fever.

COMMENT

To make the diagnosis of Fiedler's myocarditis all known causes of myocarditis must be eliminated. It was felt rheumatic myocarditis was ruled out because of the following facts: There was no history of joint involvement, subcutaneous nodules, or chorea; there was no clinical evidence of arthritis, fever, or skin rash; repeated sedimentation rates were never ele-

vated; the electrocardiogram showed no prolongation of the P-R interval; there were no mitral murmurs characteristic of rheumatic fever; there was no rise of antistreptolysin or antihyaluronidase titers (the effect of ACTH on these titers is not certain). These titers were high enough to suggest a previous streptococcal infection in that they were falling; however, from ASO

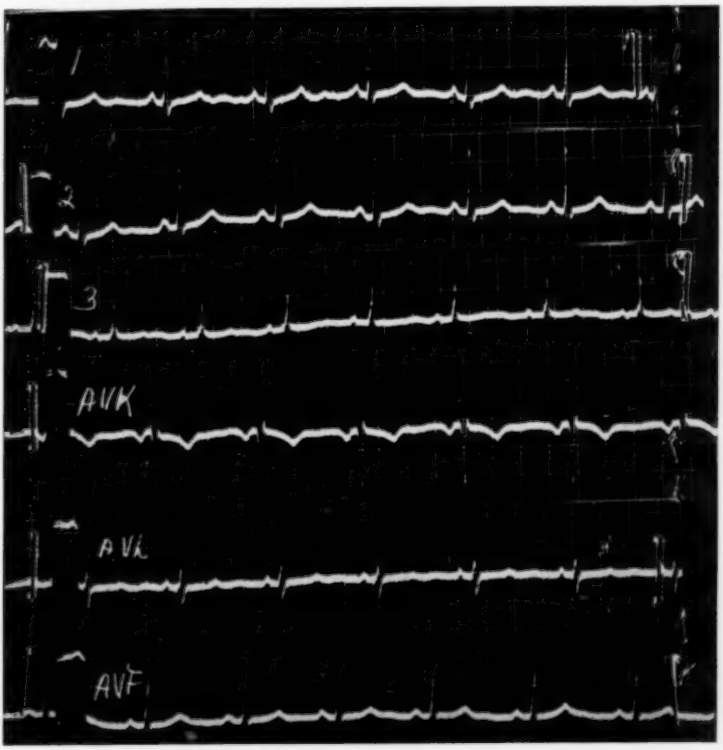

Fig. 7.—Electrocardiogram on Oct. 1, 1951.

alone one would not be impressed in this case. A poststreptococcal myocarditis is a possibility. The remainder of known causes (toxic, infectious, drug, allergic, dietary, potassium changes) were ruled out by history, physical examination, and laboratory data as much as possible. A virus etiology remains a distinct possibility, as it does in all cases of Fiedler's myocarditis. Evans and Graybiel[2] pointed out that electrocardiographic changes could be found in infectious mononucleosis. More recently, myocardial changes have been found in poliomyelitis and coxsackie infections. Of course, many of the common contagious diseases such as measles and mumps have caused myocardial damage. There was no clinical evidence of these diseases in this case but virus studies were not done.

Tedeschi and Stevenson[3] have recently reviewed the disease and reported two cases in infants. Weber, Baldwin, and Hall[4] reviewed the past literature in 1949 and presented a case history in a 10-year-old child. In all of these the diagnosis was made at autopsy.

Two clinical types are described, one with a rapid downhill course with sudden death, and the other type which progresses more slowly over a period of several weeks. Our case seems to fit the latter type. As stated by Tedeschi and Stevenson,[3] many patients die suddenly without previous illness and have been mistakenly diagnosed as status thymicolymphaticus. Careless autopsies may have overlooked the myocardial disease.

The post-mortem findings on previous cases have shown isolated myocarditis, with granulomatous or diffuse form of interstitial myocarditis. Saphir[5] has stated the endocardium and pericardium are not involved, but Kenny and Sanes[6] have reported on patients with endocardial fibrosis. Occasional eosinophilic infiltration has been reported.

It is interesting how many cases in the literature were diagnosed ante mortem as pneumonia with the heart changes believed to be secondary. This may have been putting the cart before the horse.

Numerous theories have been advanced on etiology, the foremost being virus, allergy, or drugs. All these things may produce interstitial myocarditis.

Coulter and Mareuse[7] described a case in a 14-year-old boy. They found in his myocardium elongated cells with distorted nuclei and lymphocytes in great number. They theorized that progress of the disease may be so rapid that a rheumatic origin may be hidden even at autopsy because the typical Aschoff bodies did not have time to form.

Perhaps ACTH will be more useful in this type of myocarditis than in rheumatic myocarditis. If the etiological agent of Fiedler's myocarditis is of short influence, ACTH may act to prevent dangerous myocardial damage during this period and produce a permanent cure, quite different from the relapses in rheumatic myocarditis because of the continuing presence of the injurious agent.

It appeared from this case with the numerous relapses and subsequent improvement with ACTH each time that there may be a continuing injurious agent present as in rheumatic fever.

The most remarkable thing about the improvement with ACTH was its apparent influence on the T waves in the electrocardiogram. Whether this was due to improvement of the myocardial tissue or from a change in some electrolyte of the myocardium is unknown. Other authors[8] have noticed S-T segment and T-wave changes in using ACTH on rheumatic myocarditis. It is well known that calcium and potassium may cause marked changes in the T-wave configuration.

Saphir and Gore[9] reported on thirteen cases of inflammatory coronary arteriosclerosis in young soldiers who died suddenly and unexpectedly, bringing out the point that some antecedent respiratory infection might have been the culprit but was so mild it was overlooked. The clinical course and electrocardiographic findings were not discussed. The case reported here could conceivably fall into this category, as there was no opportunity to see exactly where the disease was in the myocardium and the electrocardiogram is not that specific.

Holman and Angevine[10] reported two cases of meningococcal myocarditis with a severe sepsis picture. That myocarditis could be produced by this organism and yet not display the other findings commonly associated with it is a possibility.

The report by Friedman and others[11] recently on acute benign pericarditis treated with ACTH and cortisone was of great interest, raising the question whether or not this could be acute benign myocarditis or if such an entity really exists. The case histories were similar except for a few differences: In this case there was more of a chronic element; the sedimentation rates in their report were elevated while normal in this case; their cases were febrile while this boy was not; a friction rub was not heard as in their cases. The similarities are

as follows: Inversion of the T wave in the electrocardiogram; large heart; lack of rheumatic element; symptomatology; congestive lung changes; response to ACTH. Perhaps we are dealing with a different variety of the same thing. It is interesting that the child who had the shortest duration of illness received no ACTH in their series. Perhaps the response in our case in the long run would have been the same also without treatment; however, the clinical improvement each time was so dramatic after a relapse that we cannot help but feel the hormone was beneficial.

SUMMARY

The case history of a 7-year-old boy with myocarditis of undetermined etiology is presented. Fiedler's myocarditis is discussed and the possible causes of such a myocarditis are listed. ACTH therapy proved beneficial in the case reported. The boy was apparently cured in the follow-up study of sixteen months.

Rheumatic, toxic, and infectious, vitamin deficiency, electrolyte changes, drugs were all ruled out as well as possible by history, clinical course, and laboratory findings. Virus studies were not done.

Whether or not ACTH will prove helpful in infants with myocarditis who previously died suddenly is not known, but apparently a trial with the hormone would be advisable. Several diseases of infancy which cause large hearts and electrocardiographic changes would have to be considered in differential diagnoses, such as endocardial fibroelastosis, idiopathic hypertrophy, Bland-Garland-White disease, congenital heart disease generally, and glycogen storage of the heart.

ACTH could not in all probability cause any change in heart size or in T-wave configuration in these diseases, and this in itself might prove a help in differential diagnosis.

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SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN INFANT

Report of a Case in an Infant Born by Cesarean Section, and With No Anoxia

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TWO important causative factors of subcutaneous fat necrosis of the newborn infant are said to be trauma[1, 2] and anoxia.[3, 4] Therefore, the occurrence of this phenomenon in a baby born by elective cesarean section—with relative freedom from any apparent trauma and with no evidences of anoxia—was felt to be of some interest.

CASE REPORT

This male infant, weighing 4.2 kilograms, was delivered by cesarean section because of cephalopelvic disproportion. The mother was 24 years of age and had had one previous cesarean section for the same indication two years ago.

During the present pregnancy the mother had not attended prenatal clinics, but she had apparently had no difficulty other than slight edema about the ankles. On admission she was in early labor; the cervix was dilated approximately 2 cm., and the presentation was left occiput posterior. After an eight-hour trial of labor, a cesarean section was performed under Pontocaine spinal anesthesia. No difficulty was encountered; the infant breathed spontaneously, cried vigorously, and seemed to be entirely normal.

On physical examination at the time of admission to the nursery about thirty minutes later, the skin of the back was noted to have a "hard feeling." The next day respirations were rapid, and the rectal temperature was recorded as 101.4° F. There was slight abdominal distention, and the Moro reflex was sluggish; there were diffuse, brawny, hot, reddened, and irregularly indurated areas of skin over the upper arms, shoulders, back, buttocks, and thighs. A roentgenogram of the chest at that time was normal. He was placed in an incubator and given oxygen at 4 liters per minute; intramuscular penicillin and streptomycin were started. Within three days the temperature had returned to normal, although the peculiar changes in the skin progressed. Edema of the hands and feet appeared on the fourth day and remained for a week. Early questionable respiratory difficulty subsided after the baby was given oxygen, and its exact origin was not determined.

On the first day the hemoglobin level was 17.1 grams per cent and the white blood cells numbered 4,760 per cubic millimeter, with 58 per cent polymorphonuclear cells, 34 per cent lymphocytes, 6 per cent monocytes, and 2 per cent eosinophils. The packed cell volume was 51 per cent; the total eosinophil count was 37 per cubic millimeter. The total protein was 5.46 grams per cent, and the albumin/globulin ratio was 3.59/2.42. Chlorides were 102 meq. per liter. Blood cultures were negative; stool cultures were negative; serologic tests for syphilis were negative; and urinalysis was within normal limits. The electrocardiogram was normal.

At the age of 17 days a skin biopsy of the buttock was done and was reported as "fat necrosis" (Fig. 1). At the age of 21 days the total eosinophil count was 493 per cubic millimeter. The level of chloride was 95 meq. and that for CO_2 was 25 mM per liter.

After the first three days, the infant was afebrile and did well. The

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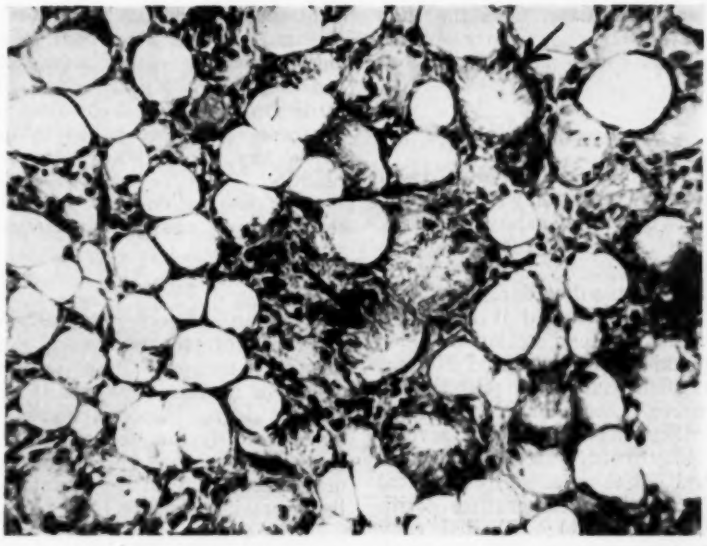

Fig. 1.—Photomicrograph of biopsy showing fat necrosis in the subcutaneous tissue. Note sheaves of crystals. (×600.) (Slides by J. Marstrander; photomicrograph by G. M. Carrera.)

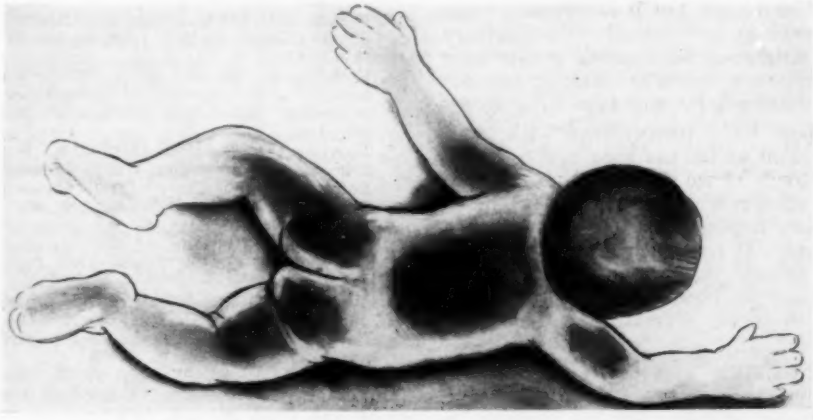

Fig. 2.—Artist's sketch of infant on twelfth day showing extent of involvement. (Drawn by Vera Morel.)

skin lesions became soft and fluctuant to feel on the twelfth day (Fig. 2); erythema persisted, but the lesions did not feel hot thereafter. At the time of discharge on the twenty-seventh day, there was still minimal residual induration.

DISCUSSION

Holzel[3] has recently reported on three newborn infants with subcutaneous fat necrosis; asphyxia being common to each, he questioned the validity of the theory that trauma is responsible for the disorder. Unshelm[4] previously had reported it in an infant born by cesarean section who also had asphyxia. Harrison and McNee[5] feel that an inflammatory process may be causative. Zeek and Madden[6] as well as others[7] have felt one or several factors may contribute, in part or alone, and list these as (1) obstetrical trauma; (2) low temperature (with solidification of fat); (3) deficiency of olein; (4) presence of an abnormal lipolytic ferment; (5) glandular dyscrasia; (6) combinations of the conditions.

That some degree of direct trauma may occur with cesarean section cannot be denied, but it is ordinarily considered to be minimal. Furthermore, subcutaneous fat necrosis is extremely uncommon even in infants severely traumatized by any type of delivery.

Low body temperature with solidification of fat has been proposed as a factor;[6, 7, 8] we could find no report of its occurrence in premature infants in whom hypopyrexia is relatively frequent. If low body temperature were a factor, then perhaps one should expect to encounter fat necrosis in hypopyrexic premature infants more often.

From the appearance of these lesions one is tempted to assume an infectious process. In our patient the very extent of involvement led initially to investigations into this possibility. We were unable to demonstrate an infectious agent by repeated cultures from the blood or from the advancing borders of the lesion.

That mobilization of depot fat increases as the concentration of 11, 17-oxycorticosteroids increases has been mentioned by Talbot.[9, 10] With this in mind we also attempted to obtain some estimation of abnormal adrenal function by eosinophil counts, electrocardiogram, and blood chemical values. In these efforts we failed to demonstrate any conspicuous adrenal dysfunction.

Our observations do not support theories of obstetrical trauma or asphyxia.

SUMMARY

In an infant with unusually extensive but nevertheless typical subcutaneous fat necrosis, there were no evidences of trauma, asphyxia of any significant degree, bacterial infection, or discernible dysfunction of the adrenal cortex. The cause and nature of this most peculiar disorder of fat metabolism remains obscure.

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AN INTRATHORACIC CYST OF ENTEROGENIC ORIGIN IN A YOUNG INFANT

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CONGENITAL mediastinal cysts can be classified according to their pathogenesis, anatomical structure, or localization. One well-defined group is formed by the so-called gastro-, entero-, and bronchogenic cysts. Nearly all of them are situated in the posterior mediastinum. The structure of the wall is similar to that of the stomach, intestine, or bronchus. Mixed types have also been described. Most investigators consider these cysts as malformations of the primitive intestine or its derivatives.

Most of the symptoms caused by these cysts are the result of pressure on surrounding organs. In the presence of secreting glands a peptic ulcer may develop. After perforation into a bronchus with arrosion of vessels, or simply as a result of venous engorgement, hemoptysis may occur. Only a few cases of successful removal of gastroenterogenic cysts have appeared in the literature.[1-8] Such an operable enterogenic cyst in an infant of 2 months came under our observation.

CASE REPORT

A. K. was the first child of healthy parents of Hungarian descent. The girl was delivered spontaneously at full term on Sept. 3, 1951. The weight was about 3,000 grams. She cried well after birth and no cyanosis was noted. Feeding proved to be difficult. She tired easily and never took more than 20 or 30 grams at a time. After a few weeks the mother developed mastitis and stopped breast feeding. A formula with buttermilk was prescribed, which was changed later on to citrated milk on account of vomiting and insufficient growth. The stools were normal at this time and were produced two or three times daily.

The parents had noted that the baby had frequent spells of coughing ever since birth and cried "as if in pain." No cyanosis was seen during the spells. A few days before admission she developed a cold. Respiration became wheezy and progressively difficult. She was brought to the hospital in an alarming condition on October 25.

We found a very ill, pale blue, dystrophic infant. The respiration was frequent and irregular. Active dilatation of the alae nasae and intracostal retraction were noted. Both inspiration and expiration were audible. The inspiration was spasmodic, the expiration prolonged. The pulse was frequent but could be easily palpated. A slight kyphoscoliosis of the cervicodorsal spine was present. Percussion sounds were dull in the region next to the right side of the heart. Over this area the respiratory sounds were thought to be diminished and crepitations were heard there. On other places the respiratory sounds were louder and prolonged and moist râles were present. Percussion of the heart seemed normal and no murmurs or other abnormalities were found on auscultation. The edge of the liver was palpable 3 cm. under the right costal margin, but could not be followed over the median line. The tip of the spleen could be felt.

Laboratory data were as follows: urine no abnormalities; hemoglobin

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content of the blood 90 per cent; erythrocytes 5.85 million per cubic millimeter; leukocytes 19.800 per cubic millimeter; differential count—rods 6 per cent, polymorphonuclears 64 per cent, lymphocytes 24 per cent, monocytes 4 per cent, and metamyelocytes 2 per cent. A slight toxic granulation was noted.

A diagnosis of lobular pneumonia and bronchiolitis was made. The baby was put in an oxygen tent and treatment with penicillin and streptomycin started in order to obtain a broad antibacterial effect in this severely ill child.

Fig. 1.—Anteroposterior view showing large heart and abnormal cervical spine.

The history indicated the possibility of a congenital malformation of the heart. An electrocardiogram showed in the third lead a W-like enlargement of the QRS complex. S-tops were obviously deep in the second lead. No definite conclusions could be drawn, but pericarditis, anomalous vessels, or myocarditis seemed unlikely.

During the following days no improvement in the labored respiration took place. When outside the oxygen tent the child became cyanosed. Feeding was very difficult. An anomaly of the respiratory tract or perhaps a foreign body in the trachea was thought possible. Examination with x-rays became necessary although this seemed a hazardous procedure. Interpretation of the x-ray pictures, made by Dr. H. E. A. Fermin, was difficult on account of the high level of the diaphragm. The heart seemed to be enlarged in all directions. Both lungs showed shadows as in lobular pneumonia (Fig. 1). The lateral view showed a rather clear-cut pear-shaped shadow in the posterior mediastinum (Figs. 2 and 3). This tumor probably was a cyst of foregut origin or a dermoid cyst. Excision was the only possibility of bringing about a cure, but the general condition was such that it could not be performed directly. Prof. Boerema then decided to try to aspirate the contents of the cyst by puncture. The puncture was carried out during fluoroscopy and yielded about 30 ml. of turbid yellow fluid. A few hours later the condition of the patient improved considerably. Administration of extra oxygen was no longer necessary and feedings could be given by bottle instead of by catheter. No tryptic activity or hydrochloric acid could be demonstrated in the aspirated fluid and no microorganisms could be isolated. There was, however, a thick layer of granulocytes in the sediment indicating inflammation. Most likely the intensive treatment with antibiotics during the preceding days had overcome the infection.

Extirpation of the cyst now seemed possible. The fact that the cyst would again accumulate fluid made it desirable not to postpone the operation and a second puncture might be less lucky than the first one. The infant was transferred to the Surgical Department on November 5, and thoracotomy was performed by Prof. Boerema on November 8. The fifth right intercostal space was opened under intratracheal anesthesia (Mrs. D. M. E. Vermeulen-Cranch). A tumor of the size of a prune became visible. It was situated in the cranial part of the

posterior mediastinum and protruded into the right pleural cavity. It was covered with parietal pleura. It was possible to isolate the smooth-walled cyst after incision of the pleura. The cyst was situated very close to the esophagus, but there was no actual attachment to it or to any other organ. A slight venous oozing from the wound bed occurred, which stopped after plugging for five minutes. The mediastinal pleura was closed with nylon

turbid fluid. The wall was grayish white and measured 3 mm. Microscopically, it consisted of an inner layer of cylindrical epithelium of the enteric type, which was ulcerating locally. Infiltration with eosinophilic granulocytes and granulation tissue was noted. More toward the periphery three muscular layers could be distinguished: a separate muscularis mucosae, and a thick double muscular layer of the intestinal type (Fig. 4).

Fig. 2.

Fig. 3.

Fig. 2.—Lateral view showing cyst and malformation of cervical spine.
Fig. 3.—Close-up of cyst during fluoroscopy.

sutures. The chest was closed, incorporating a water-sealed drain. The next day the right lung expanded satisfactorily. No hemorrhage occurred. The drain was then removed. The wound healed primarily.

Pathologic examination of the tumor by Dr. R. van Dam showed an egg-shaped cyst measuring 2½ × 3½ × 2½ cm. A few blood vessels were seen on the surface but no stalk could be found. Cross section showed an unilocular cyst, filled with mucid, slightly

The diagnosis of enterogenic cyst was made.

The epicrisis was clear. The congenital cyst, situated high in the posterior mediastinum, had impaired both the passage of food through the esophagus and of air through the trachea. Infection of the respiratory tract was followed presumably by invasion of the cyst, which caused it to enlarge, leading to a perilous restriction of space in the mediastinum with compression of the trachea. Punc-

ture brought about relief to the extent that extirpation of the cyst could be performed.

Oral feeding was again continued on November 8. No difficulties such as dyspnea or cyanosis were encountered. Two days after operation it was no longer necessary to give fluids intravenously. The number of feedings was decreased gradually, each time larger amounts being given by bottle. The increase in weight was insufficient, however, and the child was

Fig. 4.—Wall of cyst, showing muscular layers and mucosa of enteric type.

not able to regulate body temperature well. On November 23 the patient was readmitted to the Children's Clinic for treatment of the dystrophy. At this time her weight was still about 3,000 grams. We did not succeed in obtaining a satisfactory growth curve: the weight increased only 500 grams in two months. Moreover the child showed definite cyanosis when crying. The right side of the chest became increasingly prominent while the left side was flattening. The heart had by now shifted a little to the left; heart sounds were normal and the electrocardiogram showed the same deviations as before operation. Moist râles could be heard regularly, for which reason the penicillin treatment was continued. The x-ray picture of the chest still demonstrated a number of shadows as in bronchopneumonia. The heart was very large, which made evaluation of the left lung difficult. Intercostal spaces were smaller on the left side than on the right.

Apart from this it was noted that the baby had a distinctly short and stiff cervical spinal column with severe impairment of its mobility. X-rays of the spinal vertebrae showed that the bodies still consisted of two parts, which, however, is normal at that age. The bodies of the cervical vertebrae could not be distinguished as separate entities. Shoulders, elbows, and wrists demonstrated symmetrical spasms of muscles, progessively causing constraint postures. No "mirror movements" were noted. This picture was consistent with the so-called dysraphic state although a syndrome of Klippel-Feil could also be considered.

Ultimately the infection of the respiratory tract did not respond longer to penicillin or aureomycin treatment. Hyperpyrexia and acute dyspepsia developed. A few days later the baby died (January 27).

The post-mortem examination was done by Dr. R. van Dam. The most important findings were dilatation of the heart, with a small defect of the interventricular septum; a widely patent ductus arteriosus (which apparently had never caused a murmur!); emphysema of the right lung with small bronchopneumonic foci; atelectasis of the left lung, probably caused by the enlarged heart, and scoliosis of the spine with convexity to the left; engorgement of the liver. The bodies of the cervical spine could not be palpated separately. The dorsal arches proved to be intact. On microscopic examination the myelum was found to be entirely normal.

DISCUSSION

Apart from the enterogenic cyst in the posterior mediastinum this baby had congenital malformations of heart and spinal column, which probably caused the symmetrical muscle spasms. There is no uniformity of opinion concerning the pathogenesis of this type of intrathoracic cysts. Many investigators consider them to be of foregut origin, and not, as Black and Benjamin[9] state, as remnants of the omphalo-enteric duct. Keith,[9a] and Ladd and Scott[10] regard these cysts as duplicates of the esophagus. Schwarz and Williams[5] suppose a hyperactivity of the inducting substance during the development of the lung buds from the foregut. A number of cells would lose their connection with the respiratory or digestive tract and later on develop into a bronchogenic-gastrogenic or enterogenic cyst. Veeneklaas[11] was the first to stress the frequent occurrence of intrathoracic gastrogenic cysts associated with abnormalities of the spinal column. In some cases the cysts were found to adhere very closely to a vertebra. Veeneklaas and associates[7] presuppose a persistence of physiological attachments between the foregut and the primitive cord. Part of the foregut would become disconnected from the latter on development of the stomach, owing to the relatively quicker growth of the cranial part of the central nervous system and its bony covering. This hypothesis is attractive because it explains both the intrathoracic occurrence of the gastrogenic cyst together with the malformations of the spinal column. In our case, however, no connection between the cyst and the spinal column was present. The cyst lay close to the esophagus but could be isolated easily from it. The hypothesis of Veeneklaas and associates cannot explain why not all cysts are adherent to the spinal column. Bronchogenic-enterogenic and mixed types of cysts are not considered in this hypothesis although their pathogenesis must be similar to that of the gastrogenic cysts. The localization especially of bronchogenic cysts is widely variable and associated malformations of the spinal column are far less frequently demonstrable. Finally, it is not clear why in cases showing strong adhesions between gastrogenic cyst and a spinal body, the connection always happens to be to one of the cranial thoracic vertebrae. On the other hand, the "Anlage" of the stomach occurs at the level of the fourth cervical vertebra.

When adhesion of a cyst with a spinal body is met with, we consider it to be of a secondary nature as regards its pathogenesis. The primary cause must be sought in a disturbance of the early development of the embryo. The symmetrical muscle spasms of the upper limbs in our patient indicate a more central disturbance, and might be, together with the anomalies of the heart, the result of the same cause.

In our case the anamnesis did not reveal further data. The mother had been sick during the first months of pregnancy and had taken caffeine regularly because of headaches. There was no evidence of infectious diseases, x-ray treatments, or food deficiences.

SUMMARY

The case history of a 2-month-old baby girl is described; she was brought into hospital in an alarming condition, caused by an infected cyst of the posterior mediastinum. Puncture and withdrawal of about 30 ml. of fluid made surgical intervention possible. An enterogenic cyst was extirpated successfully. Other congenital deformities consisted of kyphosis and scoliosis of the spinal column, rigidity of the neck, symmetrical muscle spasms of the upper limbs. The baby remained dystrophic after operation, although respiratory function appeared to be practically normal. Atelectasis of the left lung and dilatation of the heart developed, however. Two months after operation a respiratory infection, resistant to antibiotic therapy, heart failure, and dyspepsia led to the death of the infant. At autopsy a large patent ductus arteriosus was found, which had never caused an

audible murmur during life. The cervical spinal column appeared to be amalgamated as in Klippel-Feil's syndrome. No pathological changes could be found in the myelum itself.

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FOUR RECURRENT ATTACKS OF PNEUMOCOCCUS MENINGITIS WITH RECOVERY

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A CASE of four recurrent attacks of pneumococcus meningitis with recovery in an 8-year-old male is presented. A review of the literature has been made with respect to incidence of multiple attacks of meningitis including both recurrent and relapsing attacks.

True recurrent pneumococcus meningitis is relatively rare. Prior to the advent of antisera and sulfonamides, pneumococcus meningitis s u r v i v a l s were unusual. "Prior to 1937 there were 185 reported cures."[1] It is, therefore, reasonable that we should observe cures, relapses, and recurrences with the widespread use of chemotherapy and antibiotics.

The importance of differentiating relapsing from recurrent meningitis must be stressed because of the rarity of the latter as compared with the former. Various authorities have given their criteria for each, but fundamentally the major distinguishing points coincide. Max J. Fox proposes that "relapsing meningitis is thus a repetition of the disease syndrome occurring during the convalescent period of the disease. Presumably the relapse is dependent on persistent infection which is not necessarily demonstrable by clinical symptomatology or laboratory tests. Recurring meningitis is a repetition of the disease syndrome occurring after convalescense and often after the patient has resumed his normal activities. Such a recurrence may result from:

(a) "Continued contact with the original source of infection.

(b) "Carriers.

(c) "Contact with a different antigen.

(d) "Persistent foci within the body."[2]

Since 1937 there have been approximately twenty-five papers in the literature describing one to three case reports of relapsing and recurring meningitis. Careful study of "recurrent meningitis" case reports shows that many of the attacks have probably been relapses rather than recurrences, since the signs and symptoms have reappeared during the convalescent period.

To substantiate this point, Craddock and Bowers[3] in 1941 reported four recurrent attacks of meningitis within one year. In the first attack pneumococci type 17 were identified, but in the second, the spinal fluid was sterile. The third attack revealed pneumococci type 28, but the fourth attack again revealed a sterile spinal fluid. Therefore, we might very well assume that the patient had two attacks of meningitis with two relapses.

In 1945 Traut[4] described a patient who had five recurrences of pneumococcus meningitis following a skull fracture. All five attacks occurred within four years. In the first three attacks, pneumococci type 21 were identified. On the fourth occasion, the organism was not typed; but no the fifth, pneumococci type 15 were identified. Again we might ask whether the second and third attacks might not have been relapses, thus making a total of three recurrences.

Hoyne and Schultz[5] of Chicago report that "nearly all of the patients reported with multiple attacks of meningitis have been adults." In Decemmer, 1947, the same authors reported

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This paper was presented before the Brooklyn Academy of Pediatrics in 1949.

The patient was admitted to the pediatric service of the Methodist Hospital in Brooklyn, N. Y.

five attacks of meningitis in a patient within a period of five years. These five attacks could safely be called authentic recurrences since five different organisms were recovered from the spinal fluid with each attack. On four occasions the infecting organism was a pneumococcus, each of different types. In the remaining instance, *Hemophilus influenzae* was responsible for the meningitis.

CASE REPORT

First Admission.—The patient who is the subject of this report is an 8-year-old white male who was admitted to the Methodist Hospital for the first time in August, 1943, at the age of 21 months. The history was that of a fall from a three-story window, resulting in a head injury. X-rays of the spine and skull were reported as negative. After an uneventful eleven-day hospital course, the patient was discharged with a diagnosis of concussion cerebri.

Second Admission.—Thirteen months after discharge, at age 3 years, the patient was again hospitalized with a history of persistent upper respiratory infection of six months' duration, vomiting, headache, fever, and poor appetite of twenty-four hours' duration.

Physical examination revealed a fairly well-developed, well-nourished white male, with moderate listlessness, circumoral pallor, and flushed cheeks. The temperature was 102° F., rectally; pulse 136; respirations 28. There was marked nuchal rigidity and the Kernig and Brudzinski signs were positive. The eye, ear, nose, and throat examination revealed a moderate nasopharyngitis. The remainder of the physical examination was essentially negative. A lumbar puncture was performed with the following results: spinal fluid turbid; cell count 6,400; polymorphonuclears 97 per cent; lymphocytes 1 per cent. Spinal fluid globulin was 3 plus; and sugar, no reduction. Culture of spinal fluid demonstrated pneumococci type 6. Urine was negative, and the white blood count was 37,250 with polymorphonuclears predominating. The patient was immediately given oral sulfadiazine on a four-hour schedule. The following day, the patient received one intrathecal injection of 10,000 units of penicillin with the same amount given intramuscularly, on a three-hour schedule. Repeated lumbar punctures demonstrated progressive improvement. The hospital course was uneventful. The meningeal signs gradually subsided and the patient was discharged.

Third Admission.—In March, 1947, about two and one-half years after discharge, he was readmitted with a history of vomiting, headache, fever, abdominal pain, and marked thirst of twelve hours' duration.

Physical examination showed an irrational, irritable, lethargic child in slight opisthotonus. Temperature was 102° F., rectally, pulse 90, and respirations 68. There was marked nuchal rigidity and the Kernig and Brudzinski signs were positive. Lumbar puncture revealed the following: spinal fluid appearance turbid; pressure increased; white cell count 12,921 with 98 per cent polymorphonuclears and 2 per cent lymphocytes; globulin 4 plus; sugar, no reduction. Spinal fluid culture demonstrated pneumococci type 19. Urine was normal, and white blood count was 11,100.

The patient was given penicillin intrathecally and intramuscularly. Sulfadiazine was also given orally, with sodium sulfadiazine 5 per cent solution given subcutaneously. Oxygen was required during the early stormy course. Repeated lumbar punctures revealed progressively clearing spinal fluids. X-rays of the sinuses revealed veiling of the ethmoids. On the thirty-first day of hospitalization the patient had completely recovered, and was free of all meningeal signs and was discharged as cured.

Fourth Admission.—On Jan. 30, 1949, nine months after discharge he was readmitted to the hospital for what proved to be the third attack of meningitis. On this occasion, the presenting symptoms were headache, fever, vomiting, and stiff neck of five to seven hours' duration.

Physical examination revealed a listless, but fully conscious, 7-year-old boy with a temperature of 104° F., rectally, a pulse of 144, and respirations of 40. There was nuchal rigidity and Brudzinski and Kernig signs were positive. The lumbar puncture results were as follows: spinal fluid, turbid; white cell count 1,896 with 91 per cent lymphocytes; globulin 2 plus; sugar, slight reduction. Culture of the spinal fluid demonstrated pneumococci, but the type remained unclassified. The urine was normal, and the white blood count was 28,400 with 95 per cent polymorphonuclears and 5 per cent lymphocytes.

The patient was given sulfadiazine orally, and penicillin intramuscularly on four- and three-hour schedules, respectively. The response to treatment was satisfactory and on the twelfth hospital day the patient was discharged free of meningeal signs.

Fifth Admission.—The fourth and final attack occurred one year following the third attack and five years after the first. The patient was admitted to the hospital Jan. 15, 1950, and the presenting symptoms were headache, vomiting, and fever of several hours' duration.

Physical examination revealed a well-developed, well-nourished 8-year-old boy who appeared moderately listless with a temperature of 103.4° F., rectally, pulse 140, and respirations 29. There was nuchal rigidity and Kernig and Brudzinski signs were positive. The results of the lumbar puncture were as follows: spinal fluid, slightly turbid; white cell count 344 with 96 per cent polymorphonuclears and 4 per cent lymphocytes; globulin 1 plus; sugar, moderate reduction; total proteins 27 mg. The spinal fluid culture revealed pneumococci type 21. The urine was normal, and the white blood count was 16,400 with a differential of 84 per cent polymorphonuclears and 16 per cent lymphocytes. Skull x-rays were negative.

The patient was given sulfadiazine and penicillin orally and intramuscularly, respectively. Seven days after admission, the sulfadiazine was discontinued and aureomycin instituted. The latter was discontinued after twenty-four hours. The patient was free of meningeal signs on the twelfth hospital day and was discharged as cured.

Noteworthy is the fact that four months prior to the onset of his last attack we had given him injections of both combination A and combination B type-specific pneumococcus polysaccharides for active type-specific immunization. The causative organism in the last attack, pneumococcus type 21, is not contained in either combination A or B which contains types 1, 2, 3, 5, 7, 8 plus 4, 6, 14, 18, and 19.

SUMMARY

1. Four recurrent attacks of meningitis are a great rarity.

2. One of the four attacks revealed pneumococci, type undetermined, on spinal fluid culture. The other three showed three different types of pneumococci (6, 19, and 21).

3. The first attack followed a head injury, but it was never discovered whether this resulted in a permanent atrium of infection.

4. Finally, a fourth attack of meningitis occurred in spite of the attempt at immunization with type-specific polysaccharides not including the antigen of the causative organism in the last attack.

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Medical Progress

CHILDHOOD CANCER (TUMORS, LEUKEMIA, AND HODGKIN'S DISEASE)

A Review

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CONTRARY to popular belief, cancer in children is primarily a problem for general practitioners and pediatricians and only secondarily for surgeons and radiologists. After all, the success or failure of the latter's technical therapy depends on an early diagnosis by the family physician. Unfortunately, success in children is rarer than in adults. As a result too many physicians feel that cancer in childhood is a dismal subject and that the outlook always is hopeless. This attitude is reflected by the lay public, and parents often remark that the reason they did not seek earlier treatment for their child was because they had understood that juvenile cancer and leukemia were always fatal.[1] It is true that the present treatment of some forms of cancer and leukemia is only palliative but these patients should be kept alive as long as possible in the hope that during the reprieve, more successful therapy will be discovered. Childhood cancer is no more hopeless than juvenile diabetes was before insulin. Many diabetics are alive today who would have died in coma if they had been regarded as hopeless and had been allowed sugar instead of being starved on meager diets until insulin was discovered. Sooner or later someone like Banting, who discovered insulin, will arise in the leukemia and cancer field. Even now several types of childhood cancer are completely cured if they are diagnosed and treated before it is too late.[2] Increased vigilance is necessary in order to bring these children under observation in time to effect a cure.[1] For this reason, if for none other, greater efforts must be made to know the types of cancer to which children are heir, to recognize them early, and to realize what can be done and to do it, but above all to increase research on methods of curing and, even more important, of preventing cancer.

Early diagnosis and the immediate institution of proper treatment will materially reduce the present death rate. The most important single factor in the early diagnosis of cancer is that the physician should be con-

From the Medical Record Library and the Department of Pediatrics, Duke University School of Medicine and Duke Hospital, Durham, N. C., with the greatly appreciated assistance of: Drs. E. P. Alyea, L. D. Baker, G. J. Baylin, R. H. Belser, R. B. Bost, E. H. Clark, H. W. Dargeon, Judith Farrar, W. D. Forbus, J. C. Glenn, D. W. Goddard, D. S. Johnson, L. E. Lee, Jr., H. H. Marks, L. S. Miller, R. P. Morehead, B. C. Nalle, Jr., K. L. Pickrell, R. B. Raney, R. J. Reeves, R. W. Rundles, M. P. Sullivan, Barnes Woodhall, and many others.

Presented on Dec. 12, 1950, on Cancer Day at the 47th Annual Meeting of the Asociación Medica de Puerto Rico, sponsored by the Puerto Rico Division of the American Cancer Society and the Cancer Control Program of the Department of Health of Puerto Rico, on March 19, 1951, at the Staff Meeting of the Atomic Bomb Casualty Commission, Hiroshima, on April 5, 1951, at the Thirteenth Congress of the Japanese Association of Medical Science, Tokyo, on April 11, 1951, at the Faculty of Medicine, Nagasaki University, and on May 7, 1952, at the Medical Society of the State of North Carolina, Pinehurst, N. C.

stantly on the alert for its occurrence, and that his mind should be so conditioned to suspecting its presence that he includes it in virtually every differential diagnosis.[3] The early symptoms of childhood cancer are often vague and obscure, and frequently are similar to those seen in the usual childhood diseases.[1] It is only in the late phases that the commonly described signs of anorexia, weight loss, anemia, large palpable masses, etc., are seen. To diagnose it early, one must suspect its possibility in any child with enlarged lymph nodes which have persisted beyond the usual few days when they are due to infection, intermittent fever, anorexia, weight loss, vague, persistent slowly increasing bone pain in one extremity, even though no tumor is palpable, dilatation of one pupil, especially if a white or grayish reflex is present, recurrent dizziness, headache, *vomiting without nausea*, unsteadiness of limbs, partial loss of vision, sensory changes, lack of sphincter control, bleeding from any body orifice, painless masses of any kind in any location. In other words, cancers of all types occur in children and no organ can be considered immune.[3] Most of the chemical tests are still inaccurate.[4]

Statistics seem to be a sine qua non of any paper on neoplastic conditions and unfortunately are frequently misleading. In areas in which pediatric deaths from dysentery and other infectious diseases are still many times greater than fatalities from cancer, most physicians regard malignancy with little interest as they are busy in preventing and treating the diseases which are more prevalent and which cause the highest mortality.[5] However, in many places, because of the reduction in the frequency of other pediatric conditions, cancer has become *relatively* more common.[6] For example, at Duke during the past twenty years, pertussis, typhoid, rickettsial and smallpox vaccines, and diphtheria and tetanus toxoids have almost eliminated these diseases. Rickets, scurvy, pellagra, childhood tuberculosis, and congenital syphilis have become rare. The widespread use of lactic acid evaporated milk has reduced the incidence of diarrhea and dysentery. Sulfonamide and antibiotic therapy has cured most infections without hospitalization.[7] Therefore the fact that

TABLE I. CANCER* UNDER 14 YEARS OF AGE, DUKE HOSPITAL, 1940-1949, INCLUSIVE

TYPE OR SITE	NUMBER	PER CENT
Brain	250†	21.4
Bone	111	9.5
Leukemia	107	9.1
Genitourinary	45‡	4.0
Hodgkin's disease	16	1.3
Miscellaneous	248	21.2
Benign tumors§	391	33.5
Total	1,168‖	100

*Including leukemia and Hodgkin's disease.

†Including 13 cord tumors.

‡39 Wilms', 3 ovary and 1 bladder tumor, and 2 sympathicoblastomas.

§286 hemangiomas, 26 lymphangiomas, 46 keloids and 33 papillomas.

‖7.4 per cent of the 15,780 admissions to the children's wards (exclusive of 11,472 newborn infants who had 17 tumors, chiefly angiomas).

7.4 per cent of the patients admitted to the children's wards of Duke Hospital during the past ten years had malignant or benign tumors or leukemia (Table I) merely illustrates this reduction in the other pediatric conditions. It also indicates that the medical profession in this southeastern area of the United States with twenty-three million people recognized cancer in childhood and referred the patients to this hospital. Yet the actual frequency of cancer in childhood is still

unknown because hospital statistics reflect the reputation of the institutional staff in attracting cancer patients rather than the true incidence of malignancy.

Mortality statistics reported by hospitals may also be misleading, depending as they do on early diagnosis, surgical skill, hospital care, and last but not least on the accuracy and thoroughness of the follow-up service. The most reliable fatality statistics are the data on children insured by the Metropolitan Life Insurance Company (Tables II and III).[8] In most age groups, cancer ranks next to accidents[9] as the second most common cause of death in children, being responsible for 11 per cent of the total pediatric deaths from disease. In the United States over 2,000 children die from cancer each year.[8] The fatalities are one-third higher in boys than in girls.[8]

Table II. Relative Death Rates Among Children: Metropolitan Life Insurance Company (1948-1949) (Courtesy H. H. Marks)

Cause of death	Relative death rates by ages (years)			
	1-14	1-4	5-9	10-14
Accidents	1†	1	1	1
Pneumonia and influenza	2	2	4	5
Cancer*	3	3	2	2
Rheumatic Fever	4	8	3	3
Communicable diseases	5	4	7	-
Tuberculosis	6	5	6	6
Congenital malformation	7	6	-	-
Poliomyelitis	-	-	5	4
Diarrhea	-	7	-	-

*Including leukemia and Hodgkin's disease.
†Relative death rate.

Table III. Deaths From Cancer* Under 14 Years of Age: Metropolitan Life Insurance Company, 1943-1947

Type or site	Number	Per cent
Leukemia	598	35
Brain	528	31
Genitourinary	106†	6
Bone	88	5
Gastrointestinal	67	4
Hodgkin's disease	51	3
Neck and thorax	35	2
Miscellaneous	234	14
Total	1,707	100

*Including leukemia and Hodgkin's disease.
†The majority probably were Wilms' tumors.

Although the prominence of cancer as a cause of death in children clearly points to a need for increased attention to this problem in the cancer control program, the general air of pessimism which has prevailed in the past with regard to the prognosis of many types of cancer in childhood is gradually lifting. An increased proportion of children with cancer are now receiving medical attention in the early stages of the disease rather than after long periods of delay, as was formerly the case; and an increasing number of children are surviving five to ten years after treatment.[1]

Table IV. Substances Used in Tumor Chemotherapy[12]

Type	Number
Inorganic compounds	1,004
Metal and halogen-containing organic compounds	532
Organic sulfur compounds and derivatives	577
Organic compounds	2,309
Peroxides	15
Radioactive agents	62
Miscellaneous material	532
Total	5,031

The American Academy of Pediatrics has recognized the importance of cancer in childhood and with the cooperation of the American Cancer Society and the support of the Babe Ruth Children's Cancer Foundation is circulating an informative pamphlet on the subject.[10] The establishment of the Children's Tumor Registry and

the appointment of Dr. Harold W. Dargeon as the attending pediatrician at the Memorial Hospital for Cancer and Allied Diseases in New York are indications of the increasing awareness of the significance of cancer in childhood. The growing importance of childhood cancer is best demonstrated by the fact that scarcely a number of any pediatric journal fails to have at least one article on the subject, as is indicated by the extensive bibliography of 508 articles attached to this paper, the bulk of which consists of references during the past two years.

Treatment consists, up to the present, of surgery, irradiation, nitrogen mustards, ACTH, cortisone, urethane, anticancer polysaccharides, substances which produce the Shwartzman phenomenon, folic acid antagonists (see leukemia below), and other measures.[11] Many new methods are constantly being studied in various parts of the world. The Medical Division of the Oak Ridge Institute for Nuclear Studies has an active cancer program with radioactive isotopes. Over 5,000 substances have been tested in tumor chemotherapy (Table IV).[12] However, the search must continue. After all, more than 6,000 chemicals were tried against malaria before chloroquine and primaquine were found.

Prevention is the most important phase of pediatrics but until the cause or causes of cancer are discovered, the main effort must be directed toward early diagnosis and treatment by means of the complete examination of all infants every month during the first year of life, and quarterly or semiannually thereafter, and through teaching the necessity of consulting a physician for queer and vague symptoms or swellings.

TYPES AND SITES

Although cancer may involve every system of the body in children as well as in adults, the majority of the neoplastic conditions in the children treated at Duke Hospital have been brain and bone tumors and leukemia (Table I). However, as previously stated, this distribution probably depends more on the referrals of the medical profession than on the true incidence. The facts that in the Metropolitan Life Insurance Company series of deaths (Table III), leukemia was more frequent than brain tumors, and that fatal genitourinary cases were more common than bone tumors, probably are indications of the relative mortality of these types as well as of their relative frequency. An additional reason that leukemia is less frequent than brain and bone tumors in hospital practice is that many physicians prefer to treat their patients with leukemia at home, since a more hopeless attitude toward leukemia deters many of the profession from referring these children to hospitals for expensive treatment. Of the forty-nine varieties of neoplasms reported in children, the following are described as examples:

1. *Brain tumors* are the commonest malignant tumors in children. Fifteen per cent of all brain tumors occur in children, usually over 4 years of age, rarely at birth. They are slightly more frequent in boys. The racial incidences are equal. The onset usually, but not always, is gradual with symptoms of increased intracranial pressure, i.e., *vomiting without nausea* (81 per cent),[3] headache (79 per cent),

staggering and unsteady gait (59 per cent), visual dimness (29 per cent), muscle weakness (24 per cent), squint (24 per cent), convulsions (10 per cent) (Table V).[13-20] Other signs are coma, deafness, diplopia, dizziness, exophthalmos (4 per cent; sometimes unilateral), gastric hemorrhage, glycosuria, hyperpathia (sensitivity) of the scalp, incoordination, oculogyric crises, olfactory or visual hallucinations,[21] pituitary cachexia, retro-orbital pain. Meningitis, epilepsy, poliomyelitis, and cerebral palsy may be simulated.[22] Massive hemorrhage into a brain tumor may cause sudden death.

TABLE V. BRAIN TUMOR SYMPTOMS UNDER 14 YEARS OF AGE, DUKE HOSPITAL, 1937-1948[13]

SYMPTOM	PERCENTAGE OF PATIENTS WHO HAD THESE SYMPTOMS	
	INITIALLY	EVENTUALLY
Vomiting without nausea	8	81
Headache	38	79
Staggering gait	19	59
Motor weakness	12	29
Visual dimness	5	29
Squint	5	24
Cervical pain	0	14
Other symptoms	7	14
Convulsions	6	10

The *focal* signs vary with the site of the tumor. The most common sites are the cerebellum (20 to 45 per cent) and pons (13 to 30 per cent), and the most frequent types are medulloblastomas (16 to 35 per cent) and gliomas (14 to 84 per cent) (Table VI). Most spinal tumors are gliomas.[23] Gliomas also may occur extranasally,[24] retinally, etc. The first sign of a retinal glioma usually is dilation of the pupil of the affected eye and is frequently disregarded until the tumor has grown large enough to be visible through it as a white or gray reflex ("cat's eye").[3]

Ophthalmoscopic and visual field examinations are essential; 88 per cent have choked disks. Usually ventriculography is necessary for the final diagnosis of suspected intracranial lesions. Encephalography should not be done if the intracranial pressure is markedly increased. Electroencephalography, fluorescein and radioactive diiodofluorescein, phosphorus and other elements (IV), and angiography may help locate the lesion.[25]

TABLE VI. TYPE OR SITE OF BRAIN TUMORS UNDER 14 YEARS OF AGE, DUKE HOSPITAL, 1937-1948[13]

TYPE OR SITE	PER CENT
Pontine	30
Midline cerebellar (medulloblastoma)	27
Cerebellar astrocytoma	11
Third ventricle glioma	10
Optic nerve glioma	2
Craniopharyngioma	2
Meningioma	1
Miscellaneous	17
Total	100*

*Other reports,[14, 15] using variable nomenclature, list: 84 per cent gliomas, 24 to 37 per cent astrocytomas, 20 to 35 per cent medulloblastomas, 7 to 11 per cent ependymoblastomas, 6 per cent teratomas, 6 per cent craniopharyngiomas, 3 per cent astroblastomas, 3 per cent ependymoblastomas, 3 per cent sarcomas, 2 per cent spongioblastomas, 2 per cent hemangioblastomas, 2 per cent meningiomas, Rathke's pouch cysts,[16] Cushing's syndrome,[17] neurofibromatosis,[18] epidermoids,[19] cerebral hydatid cysts,[20] etc.

2. *Bone tumors*, which are the second most frequent malignant tumors in childhood, may cause palpable masses, local swelling, pain, lameness, and restriction of joint motion. Pain localized to one area of the bony skeleton and lasting more than a few days should lead to the suspicion of a bone sarcoma.[3] X-rays, biopsy, blood phosphatase, tuberculin and serologic tests assist in the diagnosis. Of the eighteen or more varieties (Table VII), osteomas, bone cysts, osteochondromas, and giant-cell

tumors usually are benign, though the last two may become malignant. The common primary malignant bone tumors are osteogenic sarcoma and Ewing's sarcoma.[1] The bones most frequently involved are the femur, tibia, vertebrae, mandible, humerus, and maxilla, in that order. Osseous involvement may also be due to tumors of other systems, and vice versa. Solitary or multiple eosinophilic granulomas, which are benign and may be inflammatory, probably are early stages of nonlipoid reticuloendotheliosis, including some varieties of Hand-Schüller-Christian disease, Abt-Letterer-Siwe's disease, and xanthomatosis.[26] They are six times as frequent in boys as in girls. One-third affect the skull. Radiation[27] and antibiotic therapy[28] may help. Osteoid osteoma is a localized benign tumorlike bony change which may regress spontaneously; trauma may be a factor.[29] Multiple myelomas[30] and the other muscle and bone tumors[31] are rare.

TABLE VII. BONE TUMORS UNDER 14 YEARS OF AGE, DUKE HOSPITAL, 1940-1949, INCLUSIVE

TYPE	NUMBER	PER CENT
Osteoma	13	12
Angioendothelioma (Ewing)	13	12
Osteochondroma	10	9
Giant cell	10	9
Fibroma	9	8
Osteogenic sarcoma	8	7
Chondroma	8	7
Other types	40*	36
Total	111†	100

*2 adamantinomas, 2 bone cysts, 1 chondrosarcoma, 5 dermoids, 2 fibrosarcomas, 1 lymphosarcoma, 3 myomas, 1 myeloma, 4 neuroblastomas, 5 osteoid sarcomas, 4 sarcomas, 6 teratomas, 5 unrecorded.

†0.7 per cent of pediatric admissions.

3. *Leukemia (myelosis)* is the third most frequent neoplastic condition among the children admitted to Duke Hospital. It is especially common at 3 to 4 years of age. The presence of excessive numbers of abnormal leukocytes and a predominance of immature cells in smears of the peripheral blood or in the bone marrow (sternal puncture) is diagnostic. The majority are of the acute lymphatic type; the others are acute myeloblastic, monocytic or myelogenous, and a few are chronic myeloid. At least 10 per cent of patients with acute leukemia have cells so undifferentiated that morphologic classification is doubtful. Of our 107 patients (Table I), 53 per cent were lymphogenous, 40 per cent myelogenous, and 7 per cent undetermined. The usual symptoms in all forms of leukemia are pallor, weight loss, sore mouth or throat, dysphagia, bleeding gums, ulcerogangrenous stomatitis, bone destruction, bands of increased bone density,[32] petechiae, nodules, and purpuric spots. The onset may be insidious or acute. Forty-nine per cent of the patients have had a preceding infection, which may be a precipitating factor. It may resemble rheumatic fever.[33] The thymus,[34] lungs,[35] mastoid,[36] and intestines[37] may be involved, and cerebral hemorrhages may occur. Leukemia is a recessive hereditary trait, may occur in siblings,[38] and occasionally is congenital in newborn infants.[39] Chronic leukemia, chloroma (a greenish skin tumor of the face), herpes zoster,[40] and Mikulicz's syndrome (a symmetrical enlargement of the salivary and lacrimal glands)[41] are rare.

*No leukemia treatment** at present is curative,[42] but Aminopterin, A-methopterin, and other antifoles

*Many of the remedies listed here are dangerous and are still being studied. They should not be used except under investigative precautions, i.e., frequent blood counts, liver and kidney function tests, etc.

usually will prolong life the longest[43] (sometimes over one year in contrast to a mean of twenty weeks before the antifoles).[44] The daily oral or intramuscular dose of Aminopterin is 1 mg. and of A-methopterin 2.5 to 5.0 mg., continued until benefit occurs, e.g., reduction in fever, bone pain, and white blood cells, or toxic reactions, e.g., changes in the oral mucous membranes, baldness, infections, purpura, hemorrhages, hypoplasia of the bone marrow, which may require blood transfusions. The citrovorum factor may reduce its toxicity.[45] ACTH and cortisone either alone or with the antifoles may cause remissions up to thirty-three weeks[46] in lymphatic leukemia (but not in myelogenous leukemia).[47] They are useful in patients who have become resistant to A-methopterin, and the folic acid antagonists are helpful in those who have become resistant to ACTH and cortisone therapy. ACTH and cortisone also cause some of Cushing's syndrome in 85 per cent of the children treated. Urethane (ethyl carbamate) is the cheapest and safest therapy, i.e., 0.5 to 1 Gm. (orally, well diluted) b.i.d. or t.i.d. until an effect occurs (usually four to six weeks), then 1 to 2 Gm. daily for an indefinite period.[48] Triethylene melamine (TEM) has been used in oral doses of 5 to 10 mg. daily in courses of two to four days.[49] It may cause uremia.[50] Thymectomy[51] and splenectomy[52] have been tried.

4. *Genitourinary tumors: Wilms' embryonal carcinosarcoma* or mixed tumor of the kidney is the most frequent type.[53] The usual age at discovery is 2 to 3 years. It is rare after 7 years of age, though occasionally newborn infants and adults may be affected. It may cause no symptoms, and in 70 per cent of the patients is discovered only by chance during routine abdominal palpation. Abdominal pain (20 per cent), hematuria (10 per cent), increased blood pressure, diminished and difficult urination, weight loss, anemia, dyspnea, and occasionally convulsions occur. Both kidneys are equally affected,[54] but rarely bilaterally.[55] One patient had the opposite kidney involved ten years after a nephrectomy.[56] Metastases occur. If the kidney function is normal (nephritis sometimes occurs), intravenous urography is recommended; if not, retrograde urography. Biopsies should not be done. Nephrectomy is necessary as soon as possible with postoperative but not preoperative x-ray therapy. The prognosis is fair if treatment is early (up to 58 per cent survival)[57]; most of the deaths occur in the first six months after operation. Increased blood pressure and hematuria worsen the prognosis. Recurrences are frequent.[54]

Other genitourinary tumors are kidney sarcomas, cysts (congenital and echinococcus), embryomas and angiomas; pararenal teratomas[58]; peripelvic lymphatic cysts of the kidney (which may destroy it); rhabdomyosarcomas, carcinomas, fibromas,[59] polyps, leiomyomas, and other smooth muscle tumors of the bladder; fat tumors of the renal capsule; hypernephromas; sarcomas, rhabdomyosarcomas and carcinomas of the prostate; granulomas of the urethra or perineum; cysts and tumors of the ureters (including hydroureter), spermatic cord,[60] testes (seminomas, teratomas, chorionepitheliomas, even in early infancy),[61] urachus, uterus (myomas), vulva (sarcomas),[62] vagina (sarcoma botryoides [a grapelike mass], cysts, and

carcinomas), and genitals (embryonal carcinomas, myroxanthosarcomas). Metastases often are diagnosed before the primary tumor. The signs of the metastases may be nonurologic (42 per cent),[63] and have been demonstrated in bone marrow.[64] Ovarian tumors are less than 1 per cent of all childhood tumors[65]; they are multilocular and dermoid cysts, arrhenoblastomas, carcinomas, dysgerminomas, sarcomas, dermoids,[66] teratomas,[67] theca-cell tumors,[68] etc. Ovarian cysts may occur even in newborn and premature infants,[69] and may cause partial intestinal obstruction.[70] Carcinomas of the cervix[71] and other uterine tumors (myomas, chorionepitheliomas) may occur.

5. *Hodgkin's disease* is the commonest type of malignant lymphoma occurring in children. It may involve the lymph nodes in any region, especially those in the cervical and axillary area. It usually starts in the retroperitoneal and mesenteric nodes, extends to the left cervical nodes and then to the axillary, inguinal, and mediastinal nodes, and spleen. The patients generally lose weight, having recurring fever (Pel-Ebstein), and are pale. Cutaneous Hodgkin's occurs with ulceration and rapid terminal blood stream spread. In 25 per cent, the bones, especially the ribs, vertebrae, and sternum, are involved. Acute fulminating cases are rare.[72] The incidence is higher in boys. Reed-Sternberg cells in a lymph node biopsy are diagnostic. *Treatment:* If localized, the complete excision of the affected nodes, followed by x-ray therapy, occasionally is successful. Nitrogen mustards[73] (especially TEM; see leukemia above), x-ray or radium will make the patient more comfortable and may prolong life, though purpura may occur. Cortisone has been used.[74]

6. *Miscellaneous malignant tumors:* In addition to the five major varieties of neoplastic conditions in children, described above, 21 per cent of the Duke pediatric cancer cases in Table I were of the following types:

a. *Neck and thorax tumors,* which are *rare,* may cause some of the following symptoms: dyspnea, aphonia, asphyxia, stridor, cough, hiccough, cyanosis, increased sweating, pallor, tachycardia, arrhythmia, dysphagia, nausea, vomiting, weight loss, ascites, backache, convulsions, or coma. They usually can be diagnosed by rhinopharyngeal examinations, laryngoscopy, bronchoscopy, transillumination, x-ray with or without Lipiodol. The following varieties occur: congenital cysts and other tumors of the face and neck[75]; carcinoma of the cheek,[76] cystic hygromas of the neck and axillae (occasionally also in the groin); tumors of the larynx[77]; lung and bronchogenic cysts and tumors[78]; bronchogenic carcinomas of the lung[79]; tumors of the esophageal wall; mesotheliomas of the pleura[80]; alveolar-cell tumors[81]; epulis[82]; embryonic rhabdomyosarcomas[83]; fibrous sternomastoid tumors[84]; mediastinal tumors,[85] reticulosarcomas,[86] cysts and teratomas[87]; nasal, laryngeal, vocal cord, tracheal, vagal,[88] aural and antral polyps, cysts, dermoids, fibromas, neurofibromas, papillomas, sarcomas, hemangiomas, and nasopharyngiomas; carotid body, cardiac[89] and parotid[90] tumors; thymomas,[91] thymus enlargement; thyroid[92] and parathyroid[93] tumors, lymphoepitheliomas, and other nasopharyngeal tumors (with or without exophthalmos).[94]

b. *Abdominal and gastrointestinal tumors and cysts:* The commonest are Wilms' tumors, previously mentioned, and neuroblastomas (see below). Others are retroperitoneal and other teratomas[95]; mesenteric cysts[96]; intestinal lymphangiomas, lymphomas, angiomas, lipomas, fibromas, neurofibromatosis (sometimes presenting as macroglossia),[97] adenomas,[98] leiomyomas, polyps (may cause rectal bleeding)[99]; desmoids of the abdominal wall; retroperitoneal, omental, omphalomesenteric duct, pelvic, dermoid, etc., tumors and cysts; esophageal adenosarcomas and other tumors (may cause dysphagia),[100] appendiceal carcinomas,[101] and rectal carcinomas (thirty-eight reported under 15 years). These tumors may produce no symptoms and be found only on routine palpation or they may cause abdominal pain and enlargement, nausea, constipation, and ascites; rectal bleeding. Gastric carcinoma is rare in children.[102] Abdominal lymphangiomas, lymphosarcomas,[103] and lymphoblastomas[104] may be responsible for cervical, axillary, and general glandular enlargement, and sometimes may cause intussusception and obstruction. Lymphangiomas of the omentum may produce abdominal swelling and pain, and a palpable abdominal mass. Enterogenous cysts probably arise from fetal diverticula. Calcified abdominal nodes, which usually are tuberculous, may cause abdominal pain. If the *liver* is involved, jaundice and a palpable liver usually are present, e.g., liver, bile duct (choledochus) cysts[105] or tumors, echinococcus or hydatid cysts, solitary nonparasitic cysts, hemangioendotheliomas,[106] primary carcinomas,[107] primary sarcomas,[108] adenomas, hematoblastomas, hemartomas, hepatomas,[109] hamartomatous cholangiohepatomas,[110] epitheliomas, hemangioendotheliomas, teratomas,[111] mixed embryonic tumors,[112] etc., with or without cirrhosis. *Pancreatic cysts, pseudocysts, and tumors* are rare in children,[113] but pancreatic cystic fibrosis and pancreatic calculi are more common. *Splenic cysts and tumors* sometimes may be palpated.

c. *Suprarenal tumors, hyperplasia, and cysts* may be associated with gigantism, virilism, hirsutism, paroxysmal hypertension, feminization or masculinization, precocious puberty, increased height, adrenal insufficiency (due to cysts), pseudohermaphrodism (in girls due to hypersecretion of androgen; adrenogenital syndrome), arthropathy, convulsions, hyperthyroidism, ascorbic acid deficiency, intestinal obstruction, weakness, bone involvement, fever, and Cushing's syndrome.[114] *Neuroblastomas* of the suprarenal and sympathetic system (sympathogoniomas) cause increased blood pressure, hematuria, metastases to the skull, long bones, and liver and are, next to Wilms' tumors* with which they are sometimes confused, the most common malignant tumor (13 per cent) in children; immediate surgery is recommended, followed by x-ray, even if metastases (usually in the bones) have occurred.[115] Chemotherapy may help.[116] *Suprarenal rests* may cause retro-orbital tumors. *Pheochromocytomas* are characterized by hypertension, which usually but not always is paroxysmal, patches of "cotton wool exudate" and flame-shaped hemorrhages in the retina, an

*Among the children at Duke Hospital, neuroblastomas were less than half as frequent as Wilms' tumors.

increased basal metabolic rate, and other tests.[117] *Cushing's syndrome* is characterized by obesity of the face, neck, and trunk ("buffalo appearance"), cutaneous striae, osteoporosis, hypertension, sexual dystrophy, diabetes mellitus, plethoric facies, obesity, hypertrichosis, weakness, fatigability, spinal pain, polycythemia, reduced basal metabolic rate, plasma K and Cl_2, and increased plasma C_a and CO_2 (alkalosis).[17]

7. *Skin tumors* are frequent, and, as indicated in Table I, consist chiefly of benign tumors[118] of which the most common are nevi[119] (angiomas,[120] hemangiomas,[121] lymphangiomas,[122] phacomatoses[123]), keloid and warts. Hemangiomas may be associated with thrombocytopenic purpura,[124] Sturge-Weber syndrome, etc., and involve the brain[125] and spinal cord.[126] The rarer skin tumors, some of which are malignant, are carcinomas, chloromas, cylindromas, dermoid cysts, diffuse endotheliomas (Ewing), disseminated osteomas, epitheliomas,[127] fungous tumors, glomus tumors, granulomas, keratomas, leiomyomas, lipomas, leukemic tumors, lymphoblastomas, lymphosarcomas, melanomas,[128] melanoblastomas,[129] mycosis fungoides, neurofibromatosis, papillomas, paraffinomas, reticuloendotheliosis, sarcoidosis, sesame oil tumors, syringomas, neuroxanthoendotheliomas, tuberous sclerosis,[130] turban tumors,[131] xanthomas,[132] xeroderma pigmentosum,[133] acanthosis nigricans,[134] papillomatosis, and granuloma gangraenescens.[135]

CONCLUSION

If pediatricians and general practitioners will be constantly alert to the fact that childhood cancer is common and that the best chance of recovery depends on early recognition, diagnosis, and treatment, the popular conception of the hopelessness of cancer will be dispelled. If, in addition, research efforts are increased, a treatment as effective as insulin in diabetes will eventually be found.

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Psychologic Aspects of Pediatrics

THE COMICS

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NEW YORK, N. Y.

LIKE the movies and radio, the comics were first introduced as pure entertainment. Because of their great popularity they have become a potent educational force as well. They appeal to both sexes, to adults as well as children, and to persons of all cultural backgrounds. Education, economic status, and occupation influence to only a slight degree the reading of comic books and funnies. Just as many proprietors and managers read them as unskilled workers. Most comic books are directed toward boys and boy interests. At present more than 20,000,000 copies of comic magazines are sold monthly in the United States.

The outstanding feature of comic books which delights children is fast action. Here is a means of escape from the hundrum of daily routine. Comics deal with contemporary matter and with situations in their simplest form. They are easy reading, short, and each tells a story. The outcome can be awaited with confidence—in the end Good always triumphs over Evil. The pictures are humorous and the characters, for the most part, simple and uncomplicated people, who do things the child himself would like to do.

Comics are recognized as valuable aids in influencing people's understanding and attitudes. They inculcate children with common concepts, doctrines, attitudes, sentiments. They discuss racial misunderstanding and prejudice, public affairs, recent inventions, social history. Some kind of teaching is obviously being done by the comics. Even the Army has utilized this method for presenting necessary information and techniques in vivid, concise form.

Opinions differ as to the value or harm of comic books for children.

PROPORTION OF CHILDREN READING COMIC BOOKS IN 1944

AGE IN YEARS	PERCENTAGE OF POPULATION READING COMIC BOOKS REGULARLY		AVERAGE NUMBER OF COMIC BOOKS READ EACH MONTH
	MALES	FEMALES	
6 - 11	95	91	12 to 13
12 - 17	87	81	7 to 8
18 and over	41	28	6 or more

The earliest comic book, a collection of Mutt and Jeff strips published in 1911, was used as a circulation builder for a newspaper. The first week's sale was 35,000. The comic magazine in its present form appeared in 1933. A year later a comic magazine, distributed as an advertising premium, ran into a half million copies.

From the Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center, and the Department of Pediatrics, New York Infirmary.

1. Some critics point to overstimulation with material relating to sex, violence, frightening episodes, and the like. It is doubtful whether comics create deep emotional disturbances. Violence committed by adults against adults seldom frightens children. Only rarely do parents complain of children being fearful or anxious after reading comic strips. It is Bender's view that fantasying in children is a constructive approach to reality and not an escape unless indulged in to excess. It serves a useful purpose in the normal development of personality. The child's inner life may outrun his capacity for self-expression. He can, however, project his fantasy upon the characters and stories of comic books. The comics stimulate the fantasy life and help the child solve his personal and social problems.

2. Criticism is sometimes directed toward the crudeness of the drawings, stories, and language, the naive sentimentality and the simple humor. Although many of the pictures and scripts are inferior in form and content, their wide appeal must be recognized. In part at least the crudeness is necessary if prices are to be kept low. Although the language used is often coarse and the varnacular of the streets, the hero's words are usually carefully chosen and the content above reproach. Since the child generally identifies with the hero adverse effects on his use of language are probably minimal.

3. Preoccupation with the comics is said to detract from interest in more worth-while literature. This may have some validity. However, many children read good books along with the comics, others read comics for several years and then transfer their time to good books, still others who read only comics would probably otherwise read nothing at all. If shorter, cheaper books of good content were available, children might read these in addition to or in place of comics. Library circulation and book sales suggest an increase rather than a decrease in juvenile reading in the past decade or two.

4. It is argued that comics keep children from other activities and interests. Although this is true it is equally true of every form of entertainment, radio, movies, television, card playing. Time spent in any of these ways is wasted only if we believe that all of a child's time must be spent in a way which will be educationally profitable.

5. The widespread opposition of parents to comic books must be considered in evaluating their influence. Indulgence by the child, against the parents' wishes, may lead not only to disagreement and argument but to undesirable secrecy and feelings of guilt.

Several points may be made in favor of comics:

1. They are an excellent technique for propaganda, simplified teaching, and presentation of historic incidents and current topics. Publishers are taking advantage of this, and already some of the "classic comics" give picture presentations of favorite stories from Dickens, Stevenson, and others. Bible stories are also presented in this way.

2. These abridgments often stimulate enough interest for the child to go on to more serious reading. Certainly some children learn important facts and attitudes from the comics that they would get in no other way.

3. There is hardly a subject which does not lend itself to presentation through comics. Many a child's resistance and reluctance to acquiring knowledge from regular books will not hold with comic books which are regarded as entertainment.

4. Teaching can be done effectively through comics. By appealing to the child's sense of humor, by presenting extreme situations, he learns to keep out of certain types of difficulty. This is brought out in cartoons of accident prevention and the like. Advertisers have used this technique repeatedly.

5. Satisfactions which children get from comics are valuable as pure pleasure and entertainment and as a harmless outlet for their own aggressions. They identify with fabulous characters and they experience the joy which comes with the triumph of Right over Might. Crime is depicted as unattractive and unsuccessful.

6. The fact that comics are cheap and that therefore children can buy them without adult assistance gives freedom of choice and a feeling of responsibility which are in themselves valuable.

7. Children who are unable to find pleasure in intellectual or social activities may gain by reading comics.

As they mature most children come to appreciate the inadequacies of comic books. Their interest wanes and they turn to more rewarding literature. Some, however, maintain an intense interest. These may be anxious or fearful children who find relief by being able to shift their own emotional burdens to the superhuman hero who can so easily cope with them. Still others find in the comics an outlet for their aggressive impulses. Such children do not so readily give up these props and may make up a part of the adult population who continue to read comics. Most adults are merely seeking entertainment from comic strips.

The comics have high potential value as an educational medium. By and large they have not made the most of their opportunities for giving more than entertainment. Propaganda, simplified teaching, presentation of social situations and historic incidents are all within the range of subject matter for the comic book and magazine.

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THE ALLOCATION OF GAMMA GLOBULIN FOR POLIO

[So many inquiries have been made as to how gamma globulin from Red Cross blood will be allocated for polio immunization this summer, that we are publishing in full a statement issued March 12 by the Office of Defense Mobilization which is responsible for the distribution. It will be noted that each state will be furnished a certain amount on May 1, based on a formula in which the deciding factor is the number of reported cases of polio, 1947 to 1951. An additional supply will be provided to the state if the incidence in the state rises above the median for the five years. The bulk of the supply will be held in a national pool to meet epidemic needs as they arise. The total amount available is estimated at 7 million cubic centimeters by midsummer. This will provide for 1 million immunizing doses for children if the same dosage by weight is used as was used last year in the experimental study.]

This letter is to advise you of the available information regarding the expected supply, method of distribution, and use of gamma globulin in connection with poliomyelitis.

Our most recent estimates indicate that between 6 and 7 million cubic centimeters of gamma globulin will be available for protection against poliomyelitis during 1953. This estimate is in addition to that estimated to be required for measles and infectious hepatitis.

We have reasonable assurance that an amount sufficient to provide each state with an initial allotment will be available by May 1.

The Office of Defense Mobilization will authorize shipment of the material without cost and shipping charges to State Health Officers on request in accordance with the following:

A. An initial allotment of gamma globulin will be determined and furnished each state on or about May 1 within the limits of available supply at that time. This amount will be calculated on the basis of 40 c.c. times the median number of reported cases for the five-year period, 1947 to 1951.

A total basic allotment for the year will be determined for each state on the basis of 40 c.c. times the number of reported clinically diagnosed cases. Due consideration will be given to State Health Officers' requests for material over and above the initial allotment when the 1953 reported incidence appears to be likely to exceed that indicated by the five-year median.

The material to be furnished on the above basis may be used for intimate contacts of clinically diagnosed cases. Health Officers desiring to use or distribute gamma globulin for this purpose are urged to provide for the keeping of records so as to determine, in so far as possible, the effectiveness of gamma globulin for the protection of intimate contacts of clinically diagnosed cases of poliomyelitis.

As soon as the reported case data and the supply situation have been carefully rechecked we will notify you of the amount of gamma globulin you may expect to receive on or about May 1 as the initial allotment.

B. The remaining major portion of the potentially available supply of gamma globulin will be reserved in a national pool for use in epidemic or emergency situations. The definitions and criteria necessary to determine the existence of such emergency or epidemic areas are to be developed by the National Research Council's allocation panel and/or other experts selected for this purpose.

A more detailed plan for the distribution and use of gamma globulin including the necessary definitions and criteria needed to determine emergency or epidemic situations is now being developed and should be available to you by April 15.

We shall also advise you further of the supply situation and other data that may necessitate changes in the above.

W. H. AUFRANC, M.D.
Director
Health Resources Staff

News and Notes

The following pediatricians were certified in the sub-specialty of Pediatric Allergy at the examination held by the **American Board of Pediatrics** in Boston, Mass., on Feb. 25, 1953:

Dr. Walter Richard Kessler, 3975 Broadway, New York 32, N. Y.
Dr. Abe Matheson, 30 N. Michigan Ave., Chicago, Ill.
Dr. Roland Boyd Scott, Department of Pediatrics, Howard University, Washington, D. C.
Dr. Sheldon C. Siegel, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Dr. Samuel Untracht, 50 E. 78th St., New York 21, N. Y.
Dr. Ross R. Weller, 536 W. Wisconsin Ave., Milwaukee 3, Wis.

Dr. Lawrence T. Royster died Jan. 7, 1953, aged 77. From 1923 to 1942 he was professor and head of the Department of Pediatrics of the University of Virginia Medical School. He was a member of the American Pediatric Society, the American Academy of Pediatrics, and, in 1915, chairman of the Section on Pediatrics of the A.M.A.

An unusually interesting program has been prepared for the **Section on Pediatrics of the A.M.A.** at its annual meeting in New York, June 2 to 4, 1953.

The first session on Tuesday afternoon is a joint session with the Section on Roentgenology. Among the six papers to be presented are discussions of Cholecystography During the First Months of Life by Caffey and Harris of New York, The Roentgen Diagnosis of Hirschsprung's Disease by McDonald and Evans of Detroit, and Lesions of the Esophagus by Neyhauser of Boston.

Following the Chairman's address on Wednesday afternoon, there will be a Panel Discussion on the Prevention of Needless Neonatal Deaths. Participants will be Bundesen of Chicago, Public Health Aspects; Clifford of Boston, Pediatrics; Huber of Indianapolis, Obstetrics; and Latourneau of Chicago, Hospital Administration.

The final session on Thursday morning will be a Symposium on Poliomyelitis, held jointly with the Sections on Public Health and Preventive Medicine and on Physical Medicine. Among the seven who will take part are Aufranc of Washington who will discuss National Policies Relative to the Distribution of Gamma Globulin, Sabin of Cincinnati on the Present Status and Future Possibilities of a Vaccine for the Control of Poliomyelitis, and the Differential Diagnosis of Poliomyelitis by Grulee, Jr., of New Orleans.

The second annual workshop on Special Education of the Exceptional Child will be held at the **Catholic University of America**, from June 12 to 23. Lectures, discussions, and seminars will be held on the mentally retarded; cerebral palsied; deaf and hard of hearing; blind and partially seeing; socially maladjusted; speech defective; undervitalized; gifted; remedial reading; occupational therapy; tests and measurements; guidance and arts and crafts.

The Department of Pediatrics, School of Medicine, **University of California at Los Angeles**, recently assumed control and operation of the Marion Davies Children's Clinic, Los Angeles. This Clinic is a general pediatric clinic with appropriate subdivisions devoted to the care of sick infants and children in southwestern United States. Until the University Hospital of the new U.C.L.A. Medical School is completed in 1954, pediatrics will be taught to the medical students at this Clinic. Applications for pediatric internship and residency are now being accepted.

A special course in Cerebral Palsy, limited to physicians only, will be given at the **Cook County Graduate School of Medicine**, from June 15 through 26, 1953, under the direction of Dr. M. A. Perlstein, of Chicago. Enrollment in the course is limited, and all applications should be sent directly to the Registrar of the Cook County Graduate School of Medicine.

Communication regarding the **7th International Congress of Paediatrics.**

1. The congress will be held from Oct. 12 to 17, 1953, in Havana, Cuba. This is

the week following the meeting of the American Academy of Pediatrics in Miami.

2. The main topics of the conference are the following:

October 12: *Epilepsy in Infancy and Childhood*

Chairman	Dr. J. Picaza, Cuba
Relators	Prof. H. Alntroms, Sweden Prof. I. McQuarrie, U.S.A.
Correlators	Prof. W. Lennox, Boston Prof. W. Penfield, Montreal Prof. M. Perlstein, Chicago Prof. F. Escardó, Argentine

October 13: *Diagnosis of Congenital Malformations of the Heart and Great Vessels Susceptible of Surgical Treatment*

Chairman	Prof. A. Castellanos, Cuba
Relators	Prof. F. Lind, Sweden Prof. I. Chávez, Mexico
Correlators	Prof. S. Gibson, Chicago Prof. I. Steinberg, New York Prof. R. Kreutzer, Argentine Prof. H. Taussig, Baltimore Prof. B. Gasul, Chicago

October 14: *Problems of the Premature Infant*

Chairman	Dr. E. Soto Pradera, Cuba
Relators	Prof. A. Ylppö, Finland Prof. Clement Smith, Boston Prof. M. Lelong, France
Correlators	Prof. O. Poleri, Uruguay Prof. A. Monerieff, London Prof. B. Vahlquist, Sweden Prof. E. Rominger, Germany

October 15: *Complications of Primary Tuberculosis*

Chairman	Prof. T. Valledor, Cuba
Relators	Prof. A. Wallgren, Sweden Prof. E. Lincoln, U.S.A.
Correlators	Prof. R. Debré, Paris Prof. C. Cocchi, Italy Prof. S. Graham, Glasgow Prof. Seroggie, Chile

October 16: *Metabolism and Nutrition Problems*

Chairman	Prof. F. Hurtado, Cuba
Relators	Prof. P. Gyorgy, Philadelphia Prof. D. C. Darrow, U.S.A. Prof. G. Fanconi, Switzerland
Correlators	Prof. R. Ramos, Spain Prof. F. Gómez, Mexico Prof. C. Krumdieck, Peru

Besides there will be held Round Table Discussions on the following topics:

B.C.G. Vaccination. Moderator: Prof. A. Wallgren, Sweden. Secretary: Dr. A. Silva, Cuba.

Nephrosis in Children. Moderator: Prof. H. Smith, U.S.A. Secretary: Dr. E. Galán, Cuba.

Bacteriology in Infantile Diarrhea. Moderator: Prof A. Adam, Germany. Secretary: Prof. A. Aballí, Cuba.

Antibiotics. Moderator: Prof. H. Poncher, Chicago. Secretary: Dr. R. Portilla, Cuba.

Virus Diseases. Moderator: Prof. J. Stokes, Philadelphia. Secretary: Dr. J. Jordán, Cuba.

Neoplastic Diseases. Moderator: Prof. S. Farber, Boston. Secretary: Dr. R. Fusté, Cuba.

Problems of Hematology. Moderator: Prof. L. K. Diamond, Boston. Secretary: Dr. F. de Miranda, Cuba.

Paediatric Surgery. Moderator: Prof. J. Lozoya, Mexico. Secretary: Dr. A. Cardonell Salazar, Cuba.

Paediatric Endocrinology. Moderator: Prof. Bronstein, U.S.A., Secretary: Dr. Argelio Garcín López, Cuba.

The time permitted for relators is 30 minutes each; for correlators 20 minutes each; for moderators of the Round Table Conferences 20 to 30 minutes each.

3. Further there will be organized, as it was the case at the congresses in New York and Zurich, a scientific exhibition and a scientific film programme. Conference members who wish to make a contribution to the exhibition and/or the film programme are requested to notify the Organizing Committee of the Congress (Hospital Mercedes, Vedado, Havana, Cuba) as soon as possible of their intention.

4. The languages admitted at the conference are English, French, German, and Spanish. All plenary sessions will be simultaneously translated into English, French, and Spanish.

Book Reviews

Clinical Allergy. French K. Hansel, M.D., St. Louis, 1953, The C. V. Mosby Co., 1005 pages. Price $17.50.

This volume by French K. Hansel of St. Louis is presented as a complete text on the subject of general allergy. Dr. Hansel is the author of *Allergy of the Nose and Paranasal Sinus* published in 1936. The author has had extensive simultaneous experience in the fields of otolaryngology and general allergy. This text incorporates all of the important special phases of allergy as relates to otolaryngology, ophthalmology, pediatrics, and dermatology.

Of particular note is the glossary of common terms used in allergy. To the beginner in allergy, this list is invaluable.

The whole problem of the allergic patient with any of the currently accepted allergic disturbances is presented with a new technique of approach by which local and constitutional reactions may be avoided when the injection of various allergenic agents is indicated. The greater majority of allergists are unable to agree with the author's use of very high dilutions of allergenic extracts in the treatment of allergic conditions either on a specific on nonspecific basis.

Because of the author's special competence and many contributions, the chapters on the nose and sinuses are very effectively presented. The old prevailing adage "once a sinus patient, always a sinus patient" no longer obtains today. Dr. Hansel reports that 90 per cent of these patients who consult the otolaryngologist have allergy.

There is ample discussion in a number of chapters on antibiotics, the antihistamines, the aerosols, ACTH and cortisone, and their place in the symptomatic treatment of the allergic patient.

Five chapters on allergy in childhood cover the subject. The need for early diagnosis and unremitting specific therapy in children is stressed, for at least 50 per cent of adult allergy has its onset in childhood.

The responsibility of management of the allergic child rests with the parents as well as the physician. It therefore is important that every physician should adequately equip himself to cope with the problem. The author is critical of the ever-present indifference on the part of certain physicians who despite the current advances made in the allergic management of these children continue to wholly employ palliative drug therapy. Moreover, these same physicians insist that the allergic child, especially the asthmatic child, will outgrow his affliction.

Reference to personality changes associated with chronic allergy has been inadequately stressed.

The book is indeed a well-written textbook and belongs in the library of the allergist, the pediatrician, and the general practitioner.

H. G. Rapaport

On the Bringing Up of Children. Edited by John Rickman, New York, 1952, Robert Brunner Publishers, 243 pages. Price $3.00.

This is a reprint of a series of discussions by psychoanalysists, first published in 1935, intended to present the influence of psychoanalysis on the upbringing of children. Three of the five essayists and the Editor have died in the interim. Dr. Melanie Klein, one of the original group of five, presents a brief preface note, and a few additions to the bibliography have been made. Otherwise the text is unchanged.

The difficulty the reviewer has had is to find in the text any definite contribution of psychoanalysis to the subject. Thus, for example, in the first chapter by the late Ella Sharpe on "Planning for Stability" there is much good advice and discussion, but it is similar to that found in many other texts on child rearing by puericultists who have nothing in common with psychoanalytic concepts. Melanie Klein in a chapter on "Weaning" assumes a theoretical concept as a fact and on this basis lets her imagination run rather wild. Even in her writings it is difficult to deduce that psychoanalysis has contributed anything definite to the mother-infant relationship that differs from the contributions to child care made by those without psychoanalytic training and experience. The five essays proved disappointing to the reviewer who

had hoped to find in the text helpful contributions from psychoanalysis to the complicated problems of child rearing.

Poliomyelitis. Papers and Discussions presented at the 2nd International Congress, Philadelphia, 1952, J. B. Lippincott Co., 555 pages. Price $7.50.

The 2nd International Congress on poliomyelitis was held in Copenhagen in September, 1951, under the presidency of Dr. Niels Bohr. There were four Symposia on virus, the coxsackie group of viruses, differential diagnosis, and immunity and resistance, and three "Reviews" on pathology and physiology, treatment, and ecology. The speakers and discussants were recognized leaders in their respective fields assembled from many countries. The papers and discussions which were presented have been collected in this volume and hence it presents a complete review of the progress that has been made in unraveling the problems of polio since the 1st Congress held in 1948. It thus forms a most complete picture of polio as of the fall of 1951. Approximately the last third of the volume presents over thirty of the scientific exhibits that were prepared for the conference. The volume is excellently printed and splendidly illustrated. It is a summary of our present-day knowledge of the disease which should be of great value to the hundreds of workers who are engaged in working on some phase of the many problems of etiology, prevention, and treatment of poliomyelitis.

Pediatrie. Robert Debré, Marcel Lelong, and collaborators, Paris, 1952, Ernest Flammarion, Editions Médicales, 2 volumes, 2,260 pages. Price 14,500 francs (French).

A new two-volume loose-leaf pediatric text to be revised annually. Nearly forty names are listed as collaborators with Drs. Debré and Lelong, but the part or parts contributed by each are not indicated in the text or index. Each volume is divided into several sections. The first contains a section on general considerations, the newborn, the premature, avitaminosis, etc., and sections on the digestive system, with chapters on such subjects as anorexia, vomiting, the spleen and pancreas, the cardiovascular system including congenital deformities, the respiratory and the genitourinary systems, and dermatology. Volume II contains sections on tumors, syphilis, tuberculosis, metabolic diseases, blood, and the nervous system.

There are no chapters on the infectious diseases as these, it is stated in the preface, are covered in another volume of this loose-leaf collection. The references to each section are scanty and refer largely to French literature. The authors state in the preface, however, that they have tried to present the results of their own experience rather than a critical review of the work of others. For this reason we note few names in the discussion of the various diseases and conditions. The volumes are well printed and the many illustrations excellent.

Die Pflege des gesunden und des kranken Kindes. Werner Catel, ed. 4, Stuttgart, 1952, Georg Thieme, 650 pages. Price DM 39.

This is the fourth edition of a popular German text on the nursing care of the well and sick infant which first appeared in 1939. There is very little omitted that has to do with the techniques of pediatric nursing. In fact, the reviewer has the feeling the text is too expansive for general nursing use or education and its value is rather one of reference. It is of interest to a nurse or pediatrician with a good reading knowledge of German. The 336 illustrations are well chosen.

What Should I Do. A Booklet About Accidents in Children.

This is a booklet of about twenty pages prepared by the Cincinnati Pediatric Society, the Children's Hospital of Cincinnati, and the Greater Cincinnati Safety Council.

It is attractively printed in color, and in simple language tells parents "what to do" and "what NOT to do" in the case of accidents to young children. Bites, scratches, cuts, broken bones, burns, foreign bodies, head injuries, and poisons are the topics covered. At the present time when accidents kill three times as many children as pneumonia and ten times as many as tuberculosis or infantile paralysis, the stimulation of interest in accident prevention is most important. It is an excellent pamphlet and the collaboration of the three Cin-

cinnati agencies in its preparation reflects the best type of physician cooperation in community problems and responsibilities. Copies may be obtained from the Safety Council, 1203 Federal Reserve Bldg., Fourth and Race Sts., Cincinnati 2.

Fanconi and Wallgren's Textbook of Paediatrics. Edited by W. R. F. Collis, New York, 1952, Grune & Stratton, 1104 pages, 441 illustrations.

This is an English translation of the *Lehrbuch der Pädiatrie* by Fanconi of Zurich and Wallgren of Stockholm published within the year. Collis of Dublin has edited an excellent translation of the text by Kawerau. The various chapters have been written by pediatricians from a number of European clinics. In all, there are nineteen contributors, representing nine different countries, to the thirty-three chapters into which the text is divided. The text follows the usual order of discussion into growth and development, heredity, examination of the child, followed by nutrition and the newborn infant, and then taking up the various systems as blood and skeletal. A few diseases as tuberculosis and syphilis are given special chapters. Among the contributors are Salmi of Finland on growth and development, Glanzmann of Berne on heredity, van Creveld of Amsterdam on disorders of metabolism, Freudenberg of Basle on nutrition, and Salomonsen of Oslo on the blood and anemias. Fanconi contributes a number of chapters including the nervous, skeletal, and genitourinary systems, and Wallgren a number including tuberculosis and juvenile rheumatism. The chapters on the acute infectious diseases and the heart and circulatory system were written by the late Dr. A. Lichtenstein. An unusual chapter on the Diseases of Childhood Peculiar to Hot Climates is contributed by Eckstein of Ankara and formerly of Hamburg.

The above summary indicates the general character of the textbook. As a whole it is by far the best European text on pediatrics that has appeared in many years. It is not an exhaustive system filled with references but rather is similar in scope and content with such standard American texts as Mitchell-Nelson and Holt-McIntosh. There are a number of differences in classification and nomenclature than is in use in the United States, and, as might naturally be expected, the stress or importance placed on certain diseases is at times different. These are not faults but geographical differences. It is a good presentation of present-day pediatrics by European authorities.

The reviewer has found the many charts and diagrams of unusual interest. They give a better graphic presentation of some subjects than are found in the American texts and these should be of particular value to the teacher and student. While the text in all probability will not supersede the recommeded texts in our medical schools, the textbook is of decided complementary value, and should be a valuable addition to the medical school library as well as to the library of the hospital and pediatric clinics.

1953 Medical Progress. Edited by Morris Fishbein, M.D., New York, 1953, The Blakiston Co., 300 pages. Price $5.00.

This is the first volume of a proposed yearbook discussing the advances of the past year that have been made in various fields of medicine. There are sixteen separate fields discussed by competent authorities, and the Editor adds a final chapter, summing up what he considers the most important advances made in medicine during 1952. A few examples of the subjects and authors are: New and Important Drugs and Medications by Paul L. Wermer of the Council on Pharmacy and Chemistry of the A.M.A. Among these he discusses Benemid, Isoniazid, and Primaquin. Dr. Perrin H. Long discusses the Infectious Diseases; Paul D. White, Cardiology—Heart Disease; Irvine H. Page and A. C. Corcoran, Arterial Hypertension. These indicate the general character of the book. The discussions are all brief, direct, and to the point. There is not much of specific interest to the pediatrician. While medicine is constantly changing and developing, it will be interesting to see if enough progress is made in any one year in a large enough number of fields to make it worth while to continue "advances" as a yearbook.

Editor's Column

A NEW SOURCE OF ACCIDENTAL POISONING IN CHILDREN

TWO recent reports of accidental poisoning in young children from the insecticide parathion[1] focus attention on a new poison of extreme toxicity. Because of its widespread use in the last two or three years more cases in all probability will occur in widely separated parts of the country, and physicians must become aware of the treatment of this medical emergency.

Parathion is an organic phosphate which was developed by German scientists from war gases during World War II while they were searching for an insecticide to replace nicotine which had become unavailable. The formula was discovered in the files of the I.G.F. after the war, when it was placed in production in the United States and has rapidly obtained widespread use in agriculture. It is used to protect fruit, vegetables, cotton, tobacco, alfalfa, cereal grain, nuts, berries, and ornamental plants from damaging insects, and is marketed under a large number of trade names as Alkron, Niran, Thiophos, Paraphos, Plantthion, Aphamite, and at least a dozen more. All carry toxic warnings. Some ten deaths from parathion have been reported in the United States since 1949 in individuals engaged in its processing or use.[2] It was reviewed by the Council on Pharmacy and Chemistry of the A.M.A. in 1950.[3] These are the first reports of accidental poisoning fatalities in young children. One of the two cases in Connecticut and one in Washington were fatal.

The poison is extremely toxic and rapid in action and may be absorbed through the respiratory tract, alimentary tract, and through the skin. The fatal case in the New Haven report followed its aerosol use for fumigation, and the second was a 5-month-old sibling who apparently absorbed the poison three days later through the use of diapers which had been hung in a fumigated room. The fatal case in the report from Wenatchee, Washington, was a 9-month-old infant who found a can containing a pasty mixture of parathion in the yard and the route was by ingestion. In another of the Wenatchee cases two little children found a sack containing parathion in powder form, and one dumped the powder on the other's head. In this series there was another case with dermal absorption. Naturally all were due to parental carelessness.

Parathion acts by destroying the cholinesterase enzymes which permit an excess accumulation of acetylcholine in the nervous system. This produces the same effect as stimulation of the parasympathetic nerves. At first the symptoms simulate those produced by muscarine: gastrointestinal disturbances with vomiting, increased sweating and lacrimation, a rise in blood pressure and pulse rates with palpitation, bronchospasm with increased bronchial secretion, and myosis. This is followed by symptoms similar to those produced by nicotine: muscular twitchings, cramps, weakness, and incoordination. Finally symptoms of a general dysfunction of the central nervous system occur: restlessness, drowsiness, mental confusion, convulsions,

and coma. All may develop in a very short space of time.

There is one laboratory test when parathion poisoning is suspected, a reduction in the cholinesterase activity of the red blood cells and plasma. Unfortunately, few laboratories are prepared to make this test, and, second, one cannot wait to institute treatment while waiting the results of this test.

Parathion poisoning is a medical emergency. All clothing should be removed and the patient scrubbed with soap and water. If the parathion has been swallowed, copious gastric lavage should be instituted. Atropine should be immediately administered and the patient kept fully atropinized. The original dose should be several times the usual dose for weight. In the nonfatal case in the infant in the New Haven report, nearly thirty doses were administered over five days. The first dose for the infant weighing 6.8 kilograms was 0.24 mg. followed by 0.1 mg. three, six, and eight hours after the original dose. If the bronchial secretions are severe, suction and even tracheotomy may be necessary. Morphine should never be given. Some patients have recovered from parathion poisoning after hours of artificial respiration.

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3. J. A. M. A. **144**: 104, 1950.

SNAKE BITES

FEW physicians are aware that some 2,000 to 3,000 cases of poisoning from snake bites occur in the United States each year. They occur most frequently in young males, and the mortality has been variously estimated at from 10 to 35 per cent. In a series of 172 snake bites in Florida about 46 per cent were in children under 15 years. Thus they are largely in the field of pediatric accidents or emergencies.

Poisonous snakes are found in practically every part of the United States. All belong to the family Crotalidae or "pit vipers," so named because of a deep depression or "pit" between but below the level of the eyes and nostrils. The true vipers which are found in Asia and Africa are not found in the United States. There are over thirty species of the "pit viper" in this country but only a few are of real importance as a cause of snake venom poisoning. Of the true rattlesnakes the Florida diamond back, which may measure over six feet in length, is considered the most dangerous and is regarded as one of the most deadly snakes in the world. It is found in the low coastal areas of the southeastern states from the Carolinas to Florida and along the Gulf Coast almost to the Mississippi. Of even greater importance is the Texas diamond back found in the arid and semiarid regions from Arkansas and Texas westward to California. It has been stated that the Texas diamond back causes as many deaths in the United States as the other species combined. A third species, the "timber rattler" ranges from New England as far south as Florida and westward as

far as Minnesota and Kansas. It averages from three to four feet in length, and ordinarily when disturbed prefers to retreat rather than attack. The "prairie rattlesnake" is smaller and extends from the Great Plains to the Rocky Mountains and from Canada to Mexico. A fifth subspecies, the "Pacific rattler," is found along the Pacific Coast from British Columbia to lower California.

A second widely distributed species of poisonous snakes is the moccasin group. The copperhead, or highland moccasin, is extremely common and has a wide distribution from Massachusetts to Florida and westward as far as Nebraska and Texas. The cottonmouth, or water moccasin, infests the lakes and swamps of the southeastern states, along the Gulf as far as Texas, and up the Mississippi Valley as far as Missouri. The moccasin snakes are especially dangerous as they give no warning before or at the time of striking, and because they are frequently confused with the many varieties of harmless snakes which have the same habitat.

A poisonous snake can strike with accuracy for a distance equal to half its length and less accurately for a greater distance. The venom is secreted by a pair of poison glands which are specialized salivary glands, and is excreted through two hollow fangs which are folded against the roof of the mouth when the snake is at rest. At the time of striking, the fangs are thrown forward. They are twice as long as the teeth, and hence the diagnosis of a bite by a poisonous snake as contrasted with a nonpoisonous one can be based on the two distinct marks of the fang puncture.

Snake venom is a complex substance. It has been the subject of much study and more than 6,000 papers have been published on snake venoms. The venom varies as to the species and even in the same species by habitat. Venoms contain two or more toxic principles. One acts on the blood cells and coagulation, producing thrombosis, necrosis, and gangrene, while the second acts as a neurotoxin.

The action of the venom following a bite is extremely rapid. Swelling begins in a few minutes and, following a bite on the hand, the entire arm may become extremely swollen within an hour. The skin over the bite area rapidly becomes dark and purple. Signs of shock with faintness, perspiration, nausea, weak pulse, and labored respiration rapidly develop. Death has been reported as taking place within a half hour following a snake bite by a Florida diamond back.

Treatment consists of local measures to prevent the spread of the venom and the use of antivenin. A tourniquet should be applied above the site of the bite to shut off venous flow, with the usual precautions against stopping arterial flow. Longitudinal incisions are made about one-fourth inch deep at the site of the bite and suction employed to produce free bleeding. Antivenin, a serum obtained by injecting horses with rattlesnake and mocassin venoms, should be injected at the site of the bite and intramuscularly into the bitten limb. It should be used within two hours after the bite and repeated at intervals of one-half to two hours as long as there is active swelling. Children require relatively larger doses of antivenin than adults.